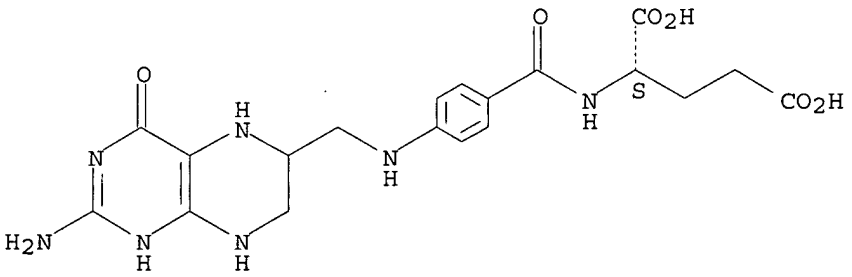
=> d

L59 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 135-16-0 REGISTRY
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, L- (7CI, 8CI)
OTHER NAMES:
CN (-)-L-5,6,7,8-Tetrahydrofolic acid
CN 5,6,7,8-Tetrahydrofolic acid
CN L-5,6,7,8-Tetrahydrofolic acid
CN **Tetrahydrofolic acid**
CN Tetrahydropteroylglutamic acid
CN THFA
FS STEREOSEARCH
DR 60201-89-0, 18632-03-6, 14231-42-6, 15582-27-1, 4172-42-3
MF C19 H23 N7 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MSDS-OHS, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

872 REFERENCES IN FILE CA (1962 TO DATE)
67 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
873 REFERENCES IN FILE CAPLUS (1962 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

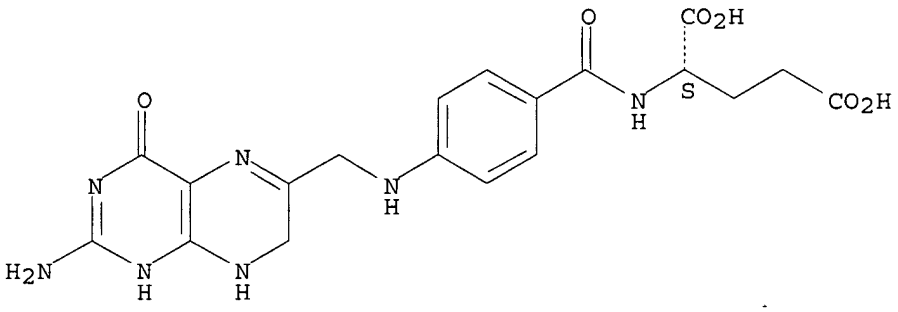
=> s dihydrofolic acid/cn
L60 1 DIHYDROFOLIC ACID/CN

=> d

L60 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 4033-27-6 REGISTRY
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2-amino-7,8-dihydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-, L- (6CI, 7CI, 8CI)
OTHER NAMES:
CN 7,8-Dihydro-L-folic acid
CN 7,8-Dihydrofolic acid
CN **Dihydrofolic acid**
FS STEREOSEARCH
MF C19 H21 N7 O6
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CHEMCATS, DDFU, DRUGU, EMBASE, MEDLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

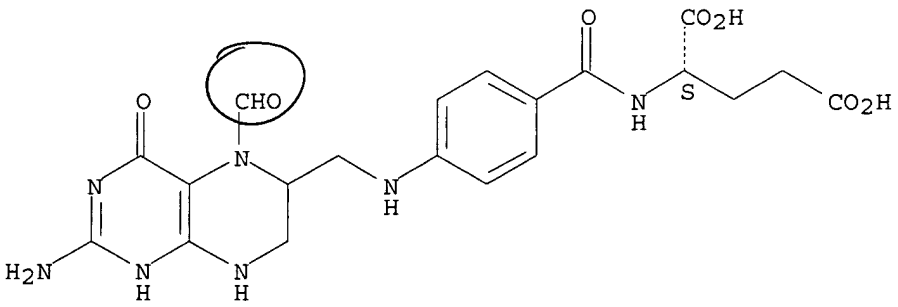


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

580 REFERENCES IN FILE CA (1962 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
580 REFERENCES IN FILE CAPLUS (1962 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L46 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 58-05-9 REGISTRY
CN L-Glutamic acid, N-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-, L- (8CI)
OTHER NAMES:
CN 10-Formyl-7,8-dihydrofolic acid
CN 5-Formyl-5,6,7,8-tetrahydrofolic acid
CN 5-Formyltetrahydrofolic acid
CN 5-Formyltetrahydropteroylglutamic acid
CN CF
CN Folinic acid
CN Folinic acid-SF
CN l-Leucovorin
CN Leucal
CN Leucoverin
CN **Leucovorin**
CN Levoleucovorin
CN N5-Formyl-5,6,7,8-tetrahydrofolic acid
CN N5-Formyltetrahydrofolic acid
CN Welcovorin
FS STEREOSEARCH
DR 641-41-8, 121521-95-7, 17435-36-8, 3102-53-2, 33299-78-4, 34786-59-9, 40244-99-3
MF C20 H23 N7 O7
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHARMASEARCH, PROMT, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1930 REFERENCES IN FILE CA (1962 TO DATE)
40 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1933 REFERENCES IN FILE CAPLUS (1962 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L12 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1994:638429 CAPLUS
DN 121:238429
TI Galenical matrixes preferably in microspherule form
IN Heinze, Friedrich; Clasen, Martina
PA Beiersdorf A.-G., Germany
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DT Patent
LA German
IC ICM A61K009-16
ICS A61K007-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 62
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 615748	A1	19940921	EP 1994-102418	19940217
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL				
	DE 4308282	A1	19940922	DE 1993-4308282	19930316 <--
	DE 4308282	C2	19941222		
	JP 07002644	A2	19950106	JP 1994-65464	19940310
	US 5496565	A	19960305	US 1994-213341	19940315
	CN 1095953	A	19941207	CN 1994-102904	19940316
PRAI	DE 1993-4308282		19930316		

AB Controlled-release matrixes for topical pharmaceuticals and cosmetics contg. .gtoreq.1 C16-22 fatty alc., .gtoreq.1 wax ester, and optionally highly disperse SiO2, formulated into microspherules, protect sensitive active agents from chem. degrdn. Thus, a melt of Ceramid HO3 3.50, Eucerite 2.50, evening primrose oil 25.00, behenyl alc. 63.50, cetyl palmitate 4.50, ascorbyl palmitate 0.50, and highly disperse SiO2 0.50 wt.% at 40-50.degree. was atomized to form 10-450-.mu.M microspherules. These microspherules 6.500, caprylic/capric triglyceride 2.500, paraffin oil 3.500, Simethicone 0.200, iso-Pr palmitate 1.500, glycerin 3.000, butylene glycol 1.500, PEG-150 2.000, acrylic acid/C10-30-alkyl acrylate copolymer 0.400, Mg/Al silicate 0.400, PVP 0.500, ZnSO4 0.400, NaOH 0.400, EtOH 1.000, citrate buffer to pH 5, and water to 100 wt.% were homogenized to form a night cream.

ST microspherule controlled release pharmaceutical cosmetic

IT Cosmetics
(microspherule matrixes; pharmaceutical and cosmetic matrixes preferably in microspherule form)

IT Waxes and Waxy substances
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical and cosmetic matrixes preferably in microspherule form)

IT Alcohols, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C16-18, pharmaceutical and cosmetic matrixes preferably in microspherule form)

IT Alcohols, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fatty, pharmaceutical and cosmetic matrixes preferably in microspherule form)

IT Alcohols, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lanolin, pharmaceutical and cosmetic matrixes preferably in microspherule form)

IT Pharmaceutical dosage forms
(microspheres, pharmaceutical and cosmetic matrixes preferably in

microspherule form)

IT 111-57-9, Ceramid 112-92-5, Stearyl alcohol 540-10-3, Cetyl palmitate 661-19-8, Behenyl alcohol 7631-86-9, Silicon dioxide, biological studies 36653-82-4, Cetyl alcohol
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical and cosmetic matrixes preferably in microspherule form)

=>

L10 ANSWER 2 OF 3 USPATFULL

AB This invention relates to the use of tetrahydrofolates in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine. Clinical areas of application include all anomalies of the homocysteine level, particularly the prevention and treatment of cardiovascular diseases and the prevention of neural tube deficiencies. The present invention also relates to pharmaceutical preparations comprising at least one compound selected from the group consisting of 5-formyl-(6S)-**tetrahydrofolic** acid, 5-methyl-(6S)-**tetrahydrofolic** acid, 5,10-methylene-(6R)-**tetrahydrofolic** acid, 5,10-methenyl-(6R)-**tetrahydrofolic** acid, 10-formyl-(6R)-**tetrahydrofolic** acid, 5-formimino-(6S)-tetra-hydrofolic acid or (6S)-**tetrahydrofolic** acid or pharmaceutically compatible salts thereof, together with pharmaceutically compatible active and adjuvant substances, for influencing the homocysteine level, particularly when a methylene tetrahydrofolate reductase deficiency exists, such as when thermolabile methylene tetrahydrofolate reductase exists for example.

ACCESSION NUMBER: 2000:1883 USPATFULL

TITLE: Use of tetrahydrofolates in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine

INVENTOR(S): Muller, Hans Rudolf, Schaffhausen, Switzerland
Ulmann, Martin, Dachsen, Switzerland
Moser, Rudolf, Schaffhausen, Switzerland

PATENT ASSIGNEE(S): Eprova AG, Schaffhausen, Switzerland (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6011040		20000104	
APPLICATION INFO.:	US 1998-95572		19980611	(9)

28. The composition of claim 6, wherein the quantity by weight of the unsaponifiable fraction in the lupine oil concentrate is about 45% to about 65%.

29. The composition of claim 11, wherein said use is selected from the group consisting of a cosmetic composition an antioxidant, an anti-free radical agent, an antielastase agent, an agent for protecting against **UVA** and/or **UVB**, and an agent for protecting **DNA** against **damage**.

ACCESSION NUMBER:	2000:153252 USPATFULL		
TITLE:	Antioxidant and/or antielastase composition based on lupine oil		
INVENTOR(S):	Msika, Philippe, Paris, France Rancurel, Alain, Leves, France Montaudoin, Marie-Georgette, Maintenon, France		
PATENT ASSIGNEE(S):	Laboratories Pharmascience, Courbevioe, France (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6146616		20001114
	WO 9847479		19981029
APPLICATION INFO.:	US 1998-202959		19981224 (9)
	WO 1998-FR827		19980424
			19981224 PCT 371 date
			19981224 PCT 102(e) date
	NUMBER		DATE
PRIORITY INFORMATION:	FR 1997-5067		19970424
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Dodson, Shelley A.		
LEGAL REPRESENTATIVE:	Foley & Lardner		
NUMBER OF CLAIMS:	29		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1025		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for tanning skin is provided in which liposomes containing a DNA repair enzyme are administered to skin in combination with exposure of the skin to **UV** radiation. The result is an enhanced level of melanin production, i.e., more tanning than achieved by **UV** radiation alone. The administration of the DNA repair enzymes in liposomes also reduces the level of **DNA damage** caused by the **UV** exposure. Accordingly, both the tanning response is increased and the deleterious effect of **UV** exposure is decreased. The method can be used by the general population as well as by individuals whose skin is susceptible to **UV** -induced damage.

ACCESSION NUMBER: 94:86190 USPATFULL
TITLE: Tanning method using DNA repair liposomes
INVENTOR(S): Yarosh, Daniel B., Merrick, NY, United States
PATENT ASSIGNEE(S): Applied Genetics Inc., Freeport, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5352458		19941004	
APPLICATION INFO.:	US 1992-995262		19921221	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kishore, G. S.
LEGAL REPRESENTATIVE: Klee, Maurice M.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 555
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 3 OF 5 USPATFULL

AB A device for measuring a total dose of biologically effective radiation is provided, in a specific embodiment, for measuring ultraviolet B radiation (**UVB**) in the wavelength range of 290-400 nm. X-radiation and high-energy particle radiation are also measurable with this device. The device includes a sample of DNA dried onto a plastic film, and the analysis method includes assaying for damage with the use of polymerase chain reaction and fluorescence techniques. The **damage** to the **DNA** is correlatable with dosage via a comparison with standardized calibration data.

ACCESSION NUMBER: 1999:43430 USPATFULL

TITLE: Radiation dosimeter and method of making and using

INVENTOR(S): Yoshida, Hiroko, Melbourne Beach, FL, United States
Regan, James D., Melbourne Beach, FL, United States

PATENT ASSIGNEE(S): Florida Institute of Technology, Melbourne, FL, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5891682		19990406	
APPLICATION INFO.:	US 1997-851634		19970506	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-16892P	19960506 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Sisson, Bradley L.

LEGAL REPRESENTATIVE: Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A.

NUMBER OF CLAIMS: 21

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 14 Drawing Figure(s); 13 Draw

L2 ANSWER 5 OF 5 USPATFULL

AB Exposing the skin to **UV** radiation interferes with the induction of the T-cell mediated immune response, including both delayed (DHS) and contact (CHS) hyper-sensitivity immune responses initiated at non-irradiated sites. The present inventors have discovered that DNA is at least one of the targets for **UV**-induced hypersensitivity, and demonstrate that the application of DNA repair enzymes can reverse the damaging effects of **UV** irradiation on both the DHS and CHS response. The usefulness of the invention in this regard was tested using a model immunosuppression system in mice. In these studies, mice were first exposed to **UV** radiation and then liposomes were used to deliver a dimer-specific excision repair enzyme to their epidermis in situ. The application of liposomal T4 endonuclease V encapsulated to the **UV**-irradiated skin both decreased the number of cyclobutane pyrimidine dimers in the epidermis and prevented suppression of both delayed and contact hypersensitivity responses. Moreover, the formation of suppressor lymphoid cells was inhibited. These studies illustrate that the delivery of lesion-specific DNA repair enzymes to living skin after **UV** irradiation is an effective tool for restoring immune function and suggest that this approach may be broadly applicable to preventing other alterations caused by **DNA damage**, including preventing or reversing viral activation (e.g., herpes virus activation), oncogene expression, or autoimmune episodes.

ACCESSION NUMBER: 94:30845 USPATFULL

TITLE: Method for treating UV-induced suppression of contact hypersensitivity by administration of T4 endonuclease

INVENTOR(S): Kripke, Margaret L., Kingwood, TX, United States
Yarosh, Daniel B., Merrick, NY, United States

PATENT ASSIGNEE(S): Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)

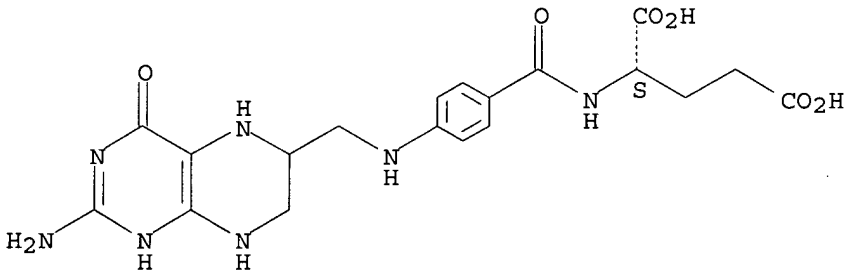
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5302389		19940412	
APPLICATION INFO.:	US 1992-931218		19920817	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Grimes, Eric
LEGAL REPRESENTATIVE: Arnold, White & Durkee
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 666
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 135-16-0 REGISTRY
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, N-[p-[[(2-amino-3,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, L- (7CI, 8CI)
OTHER NAMES:
CN (-)-L-5,6,7,8-Tetrahydrofolic acid
CN 5,6,7,8-Tetrahydrofolic acid
CN L-5,6,7,8-Tetrahydrofolic acid
CN **Tetrahydrofolic acid**
CN Tetrahydropteroylglutamic acid
CN THFA
FS STEREOSEARCH
DR 60201-89-0, 18632-03-6, 14231-42-6, 15582-27-1, 4172-42-3
MF C19 H23 N7 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MSDS-OHS, PIRA, PROMT, RTECS*, TOXCENTER, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

851 REFERENCES IN FILE CA (1967 TO DATE)
65 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
851 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

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=> s dihydrofolic acid/cn
L1            1 DIHYDROFOLIC ACID/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   4033-27-6  REGISTRY
CN   L-Glutamic acid, N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-
     pteridinyl)methyl]amino]benzoyl]- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glutamic acid, N-[p-[[(2-amino-7,8-dihydro-4-hydroxy-6-
     pteridinyl)methyl]amino]benzoyl]-, L- (6CI, 7CI, 8CI)
OTHER NAMES:
CN   7,8-Dihydro-L-folic acid
CN   7,8-Dihydrofolic acid
CN   Dihydrofolic acid
FS   STEREOSEARCH
MF   C19 H21 N7 O6
CI   COM
LC   STN Files:   ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT,
       CAOLD, CAPLUS, CHEMCATS, DDFU, DRUGU, EMBASE, MEDLINE, TOXCENTER,
       USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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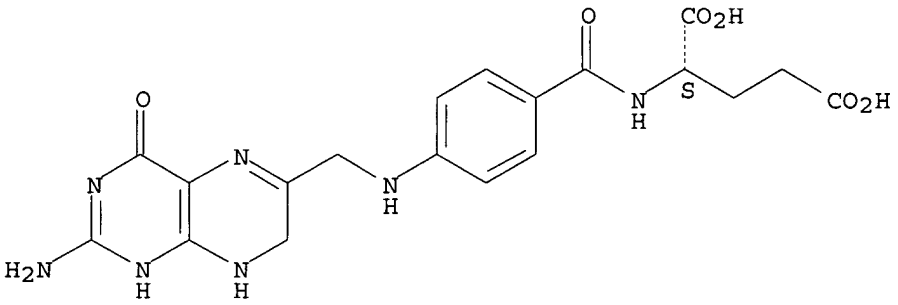


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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              23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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L2             1 S TETRAHYDROFOLIC ACID/CN

     FILE 'CAPLUS' ENTERED AT 16:00:13 ON 13 SEP 2002
L3            15 S L1/THU
L4            25 S L2/THU
L5            17 S L4 NOT L3
L6            34 S DNA INTRINSIC
L7             0 S L6 AND SKIN

     FILE 'USPATFULL' ENTERED AT 16:02:58 ON 13 SEP 2002
L8             1 S DNA INTRINSIC
L9             0 S L8 AND SKIN
L10           49 S L1 OR L2
L11           16 S L10 AND SKIN
L12          145 S DIHYDROFOLIC ACID
L13          294 S TETRAHYDROFOLIC ACID
L14           18 S L12/CLM OR L12/AB
L15           59 S L13/CLM OR L13/AB
L16           71 S L14 OR L15
L17            2 S L16 AND SKIN

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L136          0 FILE DGENE
L137          0 FILE ENCOMPPAT
L138          0 FILE ENCOMPPAT2
L139         71 FILE EUROPATFULL
L140         30 FILE IFIPAT
L141          1 FILE INPADOC
L142          1 FILE JAPIO
L143          0 FILE PAPERCHEM2
L144          0 FILE PATDD
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L147          2 FILE PATOSEP
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L149        228 FILE PCTFULL
L150          0 FILE PIRA
L151          1 FILE RAPRA
L152          0 FILE SYNTHLINE
L153          0 FILE TULSA
L154          0 FILE TULSA2
L155        218 FILE USPATFULL
L156          5 FILE USPAT2
L157         44 FILE WPIDS

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'PI' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'JAPIO'
'PI' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'PATOSDE' - USE
'PC,PN,PNW,PK,PD,PY,PMO'
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'PI' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'PCTFULL'
'PI' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'WPIDS'
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'PI' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'PATOSWO' - USE
'PC,PN,PNW,PK,PD,PY,PMO'
E1            1     DE4340999/PI
E2            1     DE4341000/PI
E3            1 --> DE4341001/PI
E4            1     DE4341002/PI
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L17 ANSWER 1 OF 2 USPATFULL

AB The present invention relates generally to the use of vitamin B12 (cobalamin or cyanocobalamin) alone or in combination with other photoprotective agents, including specifically other vitamins such as vitamin B9 (folic acid or folate) and vitamin B3 (niacin or niacinamide), or any chemical derivative of these vitamins and their salts, as a filter to protect cells against the damaging effects of ultraviolet (UV) light. The invention is, in one aspect, a method of reducing the rate of UV damage to cells exposed to a UV light source, by treating the celis with the vitamin composition, either alone or in combination with other photoprotective agents. Other aspects of the invention are compositions comprising effective amounts of vitamin B12 alone or in combination with other photoprotective agents including vitamin B9 and vitamin B3 and a pharmaceutically-acceptable carrier, that are useful in protecting cells, particularly **skin** cells, against the burning, genotoxic (mutagenic and carcinogenic), immunosuppressive and photoaging effects of UV light, especially sunlight. The invention has application as a UV light filter in oral preparations including tablets and drinks, topical creams, lotions, sprays, wipes and cosmetics. The invention also has application as a medicinal treatment for dermatological conditions caused by exposure to sunlight, such as actinic keratoses, photodermatitis, photo-induced (discoid) lupus erythematosus and the photosensitizing effects of a variety of drugs used commonly in clinical practice (e.g. certain antihistamines, ACE inhibitors, and antibiotics such as tetracycline).

SUMM [0002] Over the past several decades, the worldwide incidence of **skin** cancer has been increasing at an alarming rate. The reason for the dramatic increase in **skin** cancers that has occurred over this period and the human suffering associated with these diseases is not entirely clear. Many experts believe that it is due, at least in part, to depletion of the earth's protective ozone layer. The widespread use of sunscreens that protect against some but not all of the sun's harmful UV radiation (UVB but not UVA) has also played a role. According to the National Cancer Institute (NCI), there will be over one million new cases of **skin** cancer reported in the United States in the year 2001 and approximately 7000 deaths. This nears the total of all other cancers combined. NCI also reports that if present trends continue 40-50% of fair skinned Americans now living are expected to develop at least one type of **skin** cancer by age sixty-five. These numbers are alarming, but in regions of the world closer to the equator, the rates of **skin** cancer are even higher.

SUMM [0003] In some regions of Australia for example, the probability of non-indigenous people (most of whom are of European descent) developing **skin** cancer at some point during their lifetime approaches 100%. **Skin** cancers are now the main cause of death in Australia of all persons between the ages of 25 and 40. Worldwide, **skin** cancer is expected to become the leading cause of death due to malignant disease in the next decade.

SUMM [0004] How did this alarming situation come about? The worldwide pandemic of **skin** cancers is probably not due to a single cause but more likely is due to a number of causal factors. These include lifestyle choices (suntanning, increased outdoor leisure activities), an aging population (accumulated **skin** damage due to chronic sun exposure and decreased DNA repair capacity with age) dietary factors (folic acid is the most common nutritional deficiency in the world and other micro-nutrient deficiencies) and environmental factors (workplace hazards and depletion of the ozone layer). In addition to increased risk of **skin** cancer, exposure to sunlight has a variety of adverse effects on the human body, including erythema (burning of the **skin**), photoaging (wrinkling) and suppression of the immune system. Recently, it has also been suggested that sunlight exposure in

women might also increase the risk of neural tube defects in the developing fetus and risk of developing endometriosis (a condition characterized by invasion of the inner lining (endometrium) tissue into the outer layers of the uterus.)

SUMM [0005] Many of the effects of solar light on the human body are interrelated. For example, children who experience only a single episode of blistering sunburn in childhood (before the age of 18) double their risk of developing **skin** cancer later in life. Tanning of the **skin** was long thought to be an important component of a healthy lifestyle. It is now considered by most experts to be quite the opposite and should be more properly considered as the unhealthy appearance of sundamaged **skin**. In addition, contrary to another widely held belief, it is now well documented that tanning confers no protection whatsoever against the most serious effect of chronic sun exposure, the increased risk of **skin** cancer.

SUMM [0006] The **skin** cancers induced by sunlight can be broadly categorized into two types: melanomas and non-melanomas (basal cell and squamous). It was generally accepted for some time that exposure to UVB (the burning rays of the sun with the wavelengths ranging from 280 to 315 nm) was responsible for the induction of melanomas, the most serious form of **skin** cancer and the tumor type responsible for most deaths. This was held to be especially true in those individuals who had at least one episode of severe sunburn early in childhood. It seems likely from more recent studies, (especially an elegant series of experiments by Dr Richard Setlow reported recently to the annual meeting of the American Academy of Dermatology) that this is simply not the case. Based on spectral and mutational fingerprint analysis (each type of UV light causes a characteristic mutational pattern in target genes) Dr Setlow has suggested that melanomas are due mainly to chronic exposure to UVA. Wrongly considered by many people to be the harmless tanning rays of the sun, UVA has wavelengths between 320 and 400 nm. UVA has less energy than UVB but is more penetrating and passes through window glass and into deeper layers of the **skin** more easily.

SUMM [0007] There are several implications of this more detailed understanding of the carcinogenic potential of UVA and UVB. First, UVA light passes easily through the atmosphere and is not absorbed by the ozone layer. It is the main type of solar UV irradiation (about 95%) that reaches the surface of the earth. In the past, it was generally believed that UVA had only beneficial effects to humans such as stimulation of vitamin D formation and tanning. However, this is clearly not the case. Wavelengths in the UVA range are damaging to the **skin**, cause photoaging and are causally related to the induction of melanomas.

SUMM [0008] Second, depletion of the ozone layer and the concomitant increase in the amount of UVB light reaching the surface of the earth cannot be the explanation for the dramatic increase in melanomas seen worldwide in recent years. More likely it is due to the widespread use of sunscreen products that slow burning of the **skin** by filtering UVB and giving a false impression to the user that sun damage is not occurring. These individuals are not only at greater risk of melanoma formation but also increased risk of photoaging of the **skin** and suppression of their immune system.

SUMM [0009] Last, chronic exposure to UVA over the lifetime of an individual and not acute sunburn in childhood is now considered to be the main causative factor in the induction of melanomas, the most serious form of **skin** cancer and the type causing most deaths (six out of seven deaths due to **skin** cancer in the United States are caused by melanomas). The general implication of these findings is that tanning is unhealthy whether done in sunlight or by exposure to artificial sources

of UVA such as those used in salons. The US FDA now recommends that people avoid tanning salons altogether and that sunscreen products should contain both UVA and UVB filters.

SUMM [0010] The mechanism of UV damage to **skin** is only partly understood. The harmful effects of UVA and UVB light on human **skin** are due primarily to direct cellular damage (see Principles and Practice of Dermatology, 2nd Edition, Williams and Wilkins, Churchill/Livingston, N.Y.). Suppression of the immune system also occurs but by an indirect mechanism. The genotoxic potential of solar light resides mainly in the ability of UV to damage DNA (DNA absorbs maximally at 254 nm). UV light causes the formation of various photoproducts in the strands of the DNA molecule. The major photoproducts caused by UV light are dimers (fusions) of adjacent pyrimidines (thymine or cytosine residues) in one of the two strands of the DNA molecule. Other minor products like 6,4 photoproducts also occur. DNA is not the only target of UV light. UV also damages other cellular components such as collagen and causes photoaging of the **skin**. But the main genotoxic (mutagenic and carcinogenic) effects of UV light seem to reside in the ability of UV wavelengths to damage DNA. The cancer causing effects of UV light are can also reside in the ability of these wavelengths to impair the body's immunosurveillance system whose job it is to detect and destroy potentially malignant cells. In the absence of a properly functioning immunosurveillance system, cells harboring tumorigenic mutations caused by sunlight are more likely to proceed to malignancy. In the art, numerous screening and filtering agents have been developed over many years, to protect **skin** against the deleterious affects of UV light. These agents are applied directly to the **skin** of a subject, and are believed to prevent UV light from penetrating the epidermis by acting as "filters," thereby absorbing or otherwise dissipating the energy contained in photons of UV light. Previously it was widely accepted in the industry that agents called "sunblocks" decreased UV-induced DNA damage, and in particular, pyrimidine dimer formation by UV opaque substances. In support of this view a recent clinical study indicated that "sunblocks" such as titanium oxide significantly reduced the incidence of pre-cancerous **skin** lesions in sunlight-exposed subjects.

SUMM [0012] Para-aminobenzoic acid (pABA) was one of the first sunfiltering agents to be identified in the art. It is now seldom used because of problems with contact dermatitis. Due to widespread use of PABA over many years about 10% of all users of sunscreen products have some degree of contact sensitivity to the compound. However, esters of PABA, particularly octyl, dimethyl, para-aminobenzoic acid, do not elicit these same **skin** reactions. Other commonly used sunfilters are compounds from the salicyclate, cinnamate, benzophenone, anthranilate, and dibenzoylmethane families of molecules. It is well known in the art to combine sunfiltering agents that absorb UV light in different portions of the spectrum. However, most of these agents are synthetic chemicals not found in commonly in nature and it is not known what effects long-term use of these compounds may have on the human body.

SUMM [0013] Sunscreen compositions exert their effects through filtering or absorbing UV light so that the damaging wavelengths do not penetrate the various layers of the **skin**. To be effective, sunscreens must be present on the **skin** as a continuous film, and must remain on the surface of the **skin** throughout the period of UV exposure. One of the problems with products currently in use is that despite numerous attempts to develop topical compositions that act as sunscreen carriers and remain on the surface of the **skin** (see U.S. Pat. No. 5,087,445), sunscreens tend to rub off on towels and clothing, and wash off in perspiration, or during swimming, showering and bathing. Even if carriers are developed that remain on the surface

of the **skin** for longer periods absorption of sunscreen (and cosmetic) additives into the **skin** remains a problem. This is due to the surprising fact that many sunfiltering agents used as sunscreen and cosmetic additives themselves cause DNA damage. Titanium dioxide for example a very common additive has long been considered to be safe and effective as a sunscreening agent. This may not be the case (see Salinaro et al., 1997, "Chemical oxidation and DNA damage catalyzed by inorganic sunscreen ingredients" FEBS Lett 418:87-90). Padimate-O, another common sunscreen additive in widespread use may also be genotoxic (see P. J. McHugh and J. Knowland, 1997, "Characterization of DNA damage inflicted by free radicals from a mutagenic sunscreen ingredient and its location using an in vitro genetic reversion assay" Photochem Photbiol 66:276-281.]

SUMM [0014] A recent research article (G. J. Cameron et al., 1997, "Systemic absorption of sunscreen after topical application" The Lancet 350: 863-864) has shown that the UVA sunscreen oxybenzone, a benzophenone derivative used commonly worldwide to make sunscreen products with high sun protection factors (SPF) is absorbed systemically and excreted in human urine soon after application to the **skin**. The repeated use of a sunscreen that is absorbed systemically could pose an especially high risk to human health if the sunscreen agent is chronically genotoxic. Taken as a whole, these data suggest that many of the sunscreen agents currently in widespread human use are carcinogenic. This has added a new urgency to the development of novel non-genotoxic sunfiltering agents. These agents should not only be effective in reducing the harmful effects of UV light, but also should be safe for human use, even upon repeated usage and over a long period of time. The present invention is submitted in an attempt to address this need.

DETD [0019] The object of the invention is to provide a means of reducing the burning, genotoxic, immunosuppressive and photoaging effects of UV light by application of three common B vitamins to the **skin**

DETD [0020] The terms "vitamin B12 derivative", "folate derivative" (vitamin B9 derivative) and "niacinamide derivative" (vitamin B3), include the precursors (pro-vitamins), metabolites, derivatives, and conjugates of the parent compounds, all of which may be either naturally occurring or synthetic, as well as the salts of the compounds. Folate derivatives include polyglutamated derivatives. Results of experiments with human volunteers described below have shown that the combination folic acid, vitamin B12 and niacinamide when taken in pill form prevented sunburning for many hours. Topical application would be effective in a similar fashion. Broadly speaking, the invention provides a method for reducing or inhibiting a disease or disorder in a mammal caused by ultraviolet radiation comprising exposing the cells to an amount of at least one of vitamin B12 or B9 but preferably the two vitamins in combination with niacinamide, in appropriate concentration, which is sufficient to reduce UV damage to cells, specifically **skin** cells.

DETD [0029] The pharmaceutical compositions for use as a sunscreen for protecting the human **skin**, human hair or another surface from ultraviolet radiation include vitamin B12, niacinamide, at least one folate, and a suitable carrier. The carriers are compatible (cosmetically or otherwise) with the route of administration. The carriers for oral, parenteral, enteral, entranasal, rectal or ocular administration are preferably at least one of water, gas, a water-based liquid, an oil, a gel, an emulsion, a dispersion or a mixture thereof.

DETD [0031] The pharmaceutical compositions protect **skin**, hair and eyes from solar radiation. Suitable compositions include an oil-in-water emulsion or a water-in-oil emulsion. In a variation, the pharmaceutical composition for use as a sunscreen further includes at least one cosmetically acceptable adjuvant or additive, such as preservative, organic solvent, browning agent, antioxidant, stabilizer, emollient, silicone, alpha-hydroxy acid, demulcent, anti-foaming agent, moisturizing agent, vitamin, fragrance, ionic or nonionic thickener,

surfactant, filler, thickener, sequestrant, polymer, propellant, alkalinizing or acidifying agent, opacifier, fatty compound or colorant.

DETD [0034] The claimed invention has the advantage that administration of the vitamin mixture containing vitamin B12, such as, cobalamin, cyanocobalamin, methylcobalamin and adenosylcobalamin., a folate, and niacinamide, for the purposes of reducing UV damage to the cells of a subject can be done either topically, systemically (orally or by injection), or via a combination of routes. Systemic delivery of the vitamin mixture might afford protection to the eye, something that cannot readily be accomplished by commercially available topical sunscreens. Such a treatment might be expected to lessen the risk of cataracts induced by UV light. Secondly, protection from UV light by a naturally occurring compound may avoid exposure to chemicals that may be toxic, genotoxic (mutagenic or carcinogenic) or irritating to the subject. Thirdly, the invention provides a method to filter or absorb harmful UV rays through the use of bioavailable compounds. Bioavailable compounds are chemicals, usually from natural sources, that are readily taken up and metabolized by cells. Because these compounds are simple B complex vitamins with other known effects their ingestion or topical application may have other health benefits than those described herein. For example subjects who have taken the three vitamin formulation described herein have reported an amelioration of symptoms of a variety of dermatological conditions including acne vulgaris, actinic keratoses, photodermatitis and certain types of psoriasis "sun allergy" including discoid lupus erythematosus. This suggests the possibility of a specific treatment for photosensitivity to UV light by the invention caused by a variety of medical conditions including but not limited to xeroderma pigmentosum, albinism, or treatment by a number of drugs. The claimed invention may be used for the prevention and treatment of disorders of the **skin**, the immune system, disorders of the hematopoietic system and cancer. The invention may also be used for protecting plant cells from solar UV. The invention may be sprayed onto plants. Other features and advantages of the invention will be evident from the following description and the claims.

DETD [0051] For whole organisms, including humans, the compounds may be administered topically, by applying them to the outside **skin** or surface of the organism. Without being bound by any theory, it is suggested that the B complex vitamins used in the invention act both inside and outside the treated cells. Many types of cells are permeable to at least some of the vitamins that are used to carry out the invention. For example, mouse L1210 cells, can take up folates such as 5-methyltetrahydrofolate, by at least two mechanisms; a specific transporter in the cell membrane that operates in the micromolar range and a second transport system that takes up folates in the nanomolar range.

DETD [0055] A suitable topical carrier can be in the form of a water-in-oil emulsion; these emulsions can be thin or thick in consistency, so as to be adaptable to spray or aerosol delivery, lotions, creams, etc. Other useful carriers for topical administration include any of gases, water, water-based liquids, lotions, dispersions, oils, oil-based solutions, powder, gels, emulsions, dispersions or mixtures thereof. Some folates are water-soluble, and can be used without an oil component in the carrier. The appropriate amount of carrier can readily be determine by those skilled in the art according to the SPF desired. Hydrophobic carriers as well as hydrophilic carriers may be employed with the sunscreen compositions. Carriers to be applied to the **skin** or hair are compatible with human **skin** or hair, respectively. Ansel et al. describe many appropriate carriers for topical administration in the above-noted reference. Other appropriate carriers are disclosed in the following patents, hereby incorporated by reference: U.S. Pat. Nos. 4,401,664, 4,938,969, 5,607,622, and 5,153,230.

DETD [0056] Additional sunscreen agents known in the art may also be added to the compositions, for example, at least one additional hydrophilic or

lipophilic organic UV-A and/or UV-B sunscreen agent such as cinnamate, benzophenone, beta-carotene, and alpha-hydroxy acids. In particular, Vitamin E (alpha-tocopherol), often used in commercial **skin** care products could be incorporated into the composition.

DETD [0058] The invention also relates to a method of protecting human **skin** or hair against the deleterious effects of solar radiation by topically applying thereto an effective amount of a composition of the invention.

DETD [0061] The composition may also contain agents that promote absorption into the **skin**, for example, propylene glycol, which was used in Example 1 and 2. The folate compounds of the invention could also be administered in liposomes, or liposomes that also contain DNA repair enzymes such as AP endonuclease

DETD [0071] The pharmaceutical compositions are used to treat diseases caused by ultraviolet radiation, such as diseases or conditions of the **skin** and immune system. The pharmaceutical compositions are used to treat actinic keratoses, photodermatitis, photo-induced (discoid) lupus erthermatosus.

DETD [0074] 3. The most effective formulation was the combination 500 mcg vitamin B12, 5 mg folic acid and 500 mg niacinamide which prevented sunburning over a period of 51/2 hours. The published UVB index gave an expected time of continuous exposure to sunlight in the Edmonton AB area of 45 minutes. The maximum SPF (**skin** protection factor) was computed to be approximately 330/45=7.3.

DETD [0076] 5. These experiments have been repeated with approximately twenty human volunteers of various **skin** types ranging in age from 25 to 35 years. Most were female, one was a qualified physician, and many were qualified nurses or other healthcare professionals trained in observing symptoms of **skin** burning. Over the past year, a variety of different combinations of the three B complex vitamins were tested by exposure of these individuals to direct sunlight in locales such as Alberta Canada, Kelowna Canada, Mexico, Montego Bay Jamaica, San Diego Calif., Phoenix Ariz., Los Angeles Calif., and Honolulu, Hi. either in the course of their work or on vacation. The subjects had various **skin** types and were of many different nationalities.

DETD [0078] 7. We identify the role of folate in the repair of UVB damage in folate deficient yeast cells, human fibroblasts and in mice. Moreover we show yeast cells harboring multiple copies of the gene encoding dihydrofolate reductase are resistant to the killing effects of UV light. The experiments show an absolute requirement for folate in the normal repair of UV damaged DNA and by inference in the etiology of human **skin** cancers.

CLM What is claimed is:

17. The method of claim 16, wherein the vitamin B9 is selected from the group consisting of folic acid, **dihydrofolic acid**, **tetrahydrofolic acid**, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid, 5-10 methenyltetrahydrofolic acid, and 5-methyltetrahydrofolic acid or derivatives thereof.

19. The method of claim 18, wherein the vitamin B3 is niacinamide and the vitamin B9 is selected from the group comprising folic acid, **dihydrofolic acid**, **tetrahydrofolic acid**, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid, 5-10 methenyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid or derivatives thereof.

34. The method of claim 33, wherein the vitamin B9 is selected from the group comprising folic acid, **dihydrofolic acid**, **tetrahydrofolic acid**, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid, 5-10 methenyltetrahydrofolic acid and 5-methyltetrahydrofolic acid or derivatives thereof.

36. The method of claim 35, wherein the vitamin B3 is niacinamide and the vitamin B9 is selected from the group comprising folic acid, **dihydrofolic acid**, **tetrahydrofolic acid**, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid, 5-10 methenyltetrahydrofolic acid and 5-methyltetrahydrofolic acid or derivatives thereof.

53. The pharmaceutical composition of claim 50, wherein the vitamin B3 is niacinamide and the vitamin B9 is selected from the group consisting of folic acid, **dihydrofolic acid**, **tetrahydrofolic acid**, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid, 5-10 methenyltetrahydrofolic acid, and 5-methyltetrahydrofolic acid or derivatives thereof.

62. The composition of claim 59, wherein the vitamin B3 is niacinamide and vitamin B9 is selected from the group consisting of folic acid, **dihydrofolic acid**, **tetrahydrofolic acid**, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5-10 methylenetetrahydrofolic acid, 5-10 methenyltetrahydrofolic acid and 5-methyltetrahydrofolic acid and derivatives thereof.

71. The use of the pharmaceutical composition of claims 43, 50, 51, or 52 to treat a disease or disorder selected from the group consisting of disorders of the **skin**, disorders of the immune system or disorders of the hematopoietic system.

ACCESSION NUMBER: 2002:61252 USPATFULL
TITLE: B complex vitamin compositions that protect against cellular damage caused by ultraviolet light
INVENTOR(S): Barclay, Barry J., St. Albert, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002035087	A1	20020321
APPLICATION INFO.:	US 2001-900064	A1	20010706 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	CA 2000-2313659	20000706

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kevin S. Lemack, Nields & Lemack, 176 E. Main Street - Suite 8, Westboro, MA, 01581
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1012
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 4033-27-6 REGISTRY
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CN 7,8-Dihydrofolic acid
CN **Dihydrofolic acid**
FS STEREOSEARCH
MF C19 H21 N7 O6
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CHEMCATS, DDFU, DRUGU, EMBASE, MEDLINE, TOXCENTER, USPATFULL
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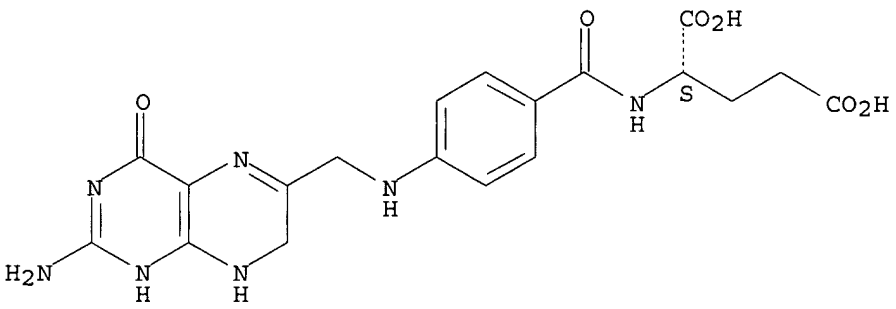

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23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
564 REFERENCES IN FILE CAPLUS (1967 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L2 1 TETRAHYDROFOLIC ACID/CN

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L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 135-16-0 REGISTRY
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)
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CN 5,6,7,8-Tetrahydrofolic acid
CN L-5,6,7,8-Tetrahydrofolic acid

CN **Tetrahydrofolic acid**
CN Tetrahydropteroylglutamic acid
CN THFA
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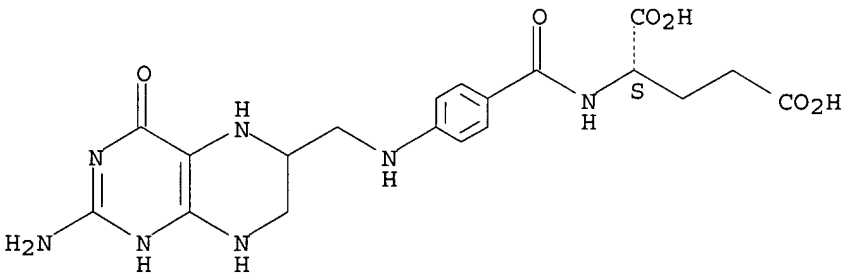

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

850 REFERENCES IN FILE CA (1967 TO DATE)
65 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
851 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 68-19-9 REGISTRY
CN **Vitamin B12 (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
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CN 5,6-Dimethylbenzimidazolyl cyanocobamide
CN 5,6-Dimethylbenzimidazolyl-Co-cyanocobamide
CN Anacobin
CN Antipernicin
CN B-Twelve
CN B-Twelve Ora
CN Bedodeka
CN Bedoz
CN Behepan
CN Berubi
CN Berubigen
CN Betalin 12
CN Betalin 12 Crystalline
CN Betaline 12
CN Betolvex
CN Byladoce
CN CN-B12
CN Cobalamin, cyanide
CN Cobalamin, cyano-
CN Cobalamin, cyano-5,6-dimethylbenzimidazole-
CN Cobalin
CN Cobamide, .alpha.-5,6-dimethyl-1H-benzimidazolyl-, cyanide
CN Cobamide, cyano-5,6-dimethyl-1H-benzimidazole-
CN Cobamin
CN Cobinamide, cyanide, dihydrogen phosphate (ester), inner salt, 3'-ester with 5,6-dimeth

L9 ANSWER 17 OF 116 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:553662 CAPLUS
DN 127:195266
TI Photostable, emulsifier-free cosmetic compositions
IN Finkel, Peter; Voss, Eckart; Urban, Werner
PA Sara Lee/de N.V., Neth.
SO Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K007-42
CC 62-4 (Essential Oils and Cosmetics)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 787483	A1	19970806	EP 1996-203629	19961219
	EP 787483	B1	20030416		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	DE 19547634	A1	19970821	DE 1995-19547634	19951220
	AT 237302	E	20030515	AT 1996-203629	19961219
	AU 9676422	A1	19970626	AU 1996-76422	19961220
	AU 720481	B2	20000601		
PRAI	DE 1995-19547634	A	19951220		

AB Photostable cosmetic compns. for protecting the human skin against skin damages caused by light, on the basis of emulsifier-free **emulsions** (**hydrodispersion** gels) for stabilizing dibenzoylmethane derivs., in particular 1-(4-tert-butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione against photodecompn. caused by UV are disclosed. A cosmetic gel contained Eusolex-6300 2.0, Parsol-1789 2.0, Finsol TN 10.0, perfume oil 0.4, preservative q.s., Carbomer 0.4, glycerin 4.0, EDTA 0.1, and water q.s. 100%.
ST photostable cosmetic gel dibenzoylmethane deriv stabilizer; Eusolex 6300 Parsol 1789 cosmetic gel
IT Cosmetics
(gels; photostable, emulsifier-free cosmetic compns.)
IT Sunscreens
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(photostable, emulsifier-free cosmetic compns.)
IT 118-56-9, 3,3,5-Trimethyl-cyclohexylsalicylate 118-56-9, Eusolex HMS 118-60-5, Salicylic acid-2-ethylhexylester 118-60-5, Neo Heliopan OS 131-57-7, 2-Hydroxy-4-methoxybenophenone 4065-45-6 5997-53-5 6197-30-4, Neo Heliopan 303 6628-37-1 10020-01-6 10380-41-3, 2-Cyano-3,3-diphenylacrylic acid 36861-47-9, Eusolex-6300 56039-58-8 56039-58-8D, salts 70356-09-1, Parsol 1789 88122-99-0, Uvinul t 150 92761-26-7 92761-26-7D, salts 94134-93-7, 4-Isopropylbenzyl salicylate 158099-19-5
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(photostable, emulsifier-free cosmetic compns.)

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L36 ANSWER 5 OF 7 USPATFULL on STN

SUMM [0117] dermally applicable oily or oil-soluble vitamins or vitamin derivatives: e.g. vitamin A (getinol in the form of the free acid or its derivatives), panthenol, pantothenic acid, **folic** acid, and combinations thereof, vitamin E (tocopherol), F; essential fatty acids; or niacin-amide (nicotinic acid amide);

SUMM [0118] vitamin-based placenta extracts: active agent compositions mainly with vitamin A, C, E, B.sub.21 B.sub.12, **folic** acid and biotin, amino acids and enzymes and also compounds of the trace elements magnesium, silicium, phosphorus, calcium, manganese, iron or copper.

SUMM [0168] Gels are semisolid, more or less transparent systems in which the so-called gel former forms a three-dimensional network in which a liquid is immobilised. The clear to opaque **hydrogels** consist primarily of water, water-soluble substances and thickeners or gel formers. If lipids are additionally incorporated, the slightly creamy-looking **hydrodispersion** gels are obtained. In contrast, the oleogels are free of water and contain lipids as liquid components.

PI US 2002106390 A1 20020808

SUMM The active ingredient used according to the invention can advantageously be incorporated into customary cosmetic and dermatological preparations, which can exist in various forms. They can, for example, be a solution, an emulsion of the water-in-oil (W/O) type or of the oil-in-water (O/W) type, or a multiple emulsion, for example of the water-in-oil-in-water (W/O/W) type or oil-in-water-in-oil (O/W/O) type, a **hydrodispersion** or lipodispersion, a gel, a solid stick or an aerosol.

SUMM The antioxidants are advantageously selected from the group consisting of amino acids (for example glycine, histidine, tyrosine, tryptophan) and derivatives thereof, imidazoles (e.g. urocanic acid) and derivatives thereof, peptides such as D,L-carnosine, D-carnosine, L-carnosine and derivatives thereof (e.g. anserine), carotenoids, carotenes (e.g. .alpha.-carotene, .beta.-carotene, lycopene) and derivatives thereof, lipoic acid and derivatives thereof (e.g. dihydrolipoic acid), aurothioglucose, propylthiouracil and other thiols (e.g. thioredoxin, glutathione, cysteine, cystine, cystamine and the glycosyl, N-acetyl, methyl, ethyl, propyl, amyl, butyl and lauryl, palmitoyl, oleyl, .gamma.-linoleyl, cholesteryl and glyceryl esters thereof) and salts thereof, dilauryl thiodipropionate, distearyl thiodipropionate, thiodipropionic acid and derivatives thereof (esters, ethers, peptides, lipids, nucleotides, nucleosides and salts) and sulphoximine compounds (e.g. buthionine sulphoximines, homocysteine sulphoximine, buthionine sulphones, penta-, hexa-, heptathionine sulphoximine) in very small tolerated doses (e.g. pmol to .mu.mol/kg), also (metal) chelating agents (e.g. .alpha.-hydroxy fatty acids, palmitic acid, phytic acid, lactoferrin), .alpha.-hydroxy acids (e.g. citric acid, lactic acid, malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and derivatives thereof, unsaturated fatty acids and derivatives thereof (e.g. .gamma.-linolenic acid, linoleic acid, oleic acid), **folic** acid and derivatives thereof, ubiquinone and ubiquinol and derivatives thereof, vitamin C and derivatives (e.g. ascorbyl palmitate, Mg ascorbyl phosphate, ascorbyl acetate), tocopherols and derivatives (e.g. vitamin E acetate), and coniferylbenzoate of benzoin, rutinic acid and derivatives thereof, ferulic acid and derivatives thereof, butylated hydroxytoluene, butylated hydroxyanisole, nordihydroguaiac resin acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and derivatives thereof, mannose and derivatives thereof, zinc and derivatives thereof (e.g. ZnO, ZnSO.sub.4), selenium and derivatives thereof (e.g. selenium methionine), stilbenes and derivatives thereof (e.g. stilbene oxide, trans-stilbene oxide) and the derivatives (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides and lipids) of said active ingredients which are suitable according to the invention.

SUMM The oil phase of the emulsions, oleogels or **hydrodispersions** or lipodispersions for the purposes of the present invention is advantageously selected from the group consisting of esters of saturated and/or unsaturated, branched and/or unbranched alkanecarboxylic acids having a chain length of from 3 to 30 carbon atoms, and saturated and/or unsaturated, branched and/or unbranched alcohols having a chain length of from 3 to 30 carbon atoms, from the group consisting of esters of aromatic carboxylic acids and saturated and/or unsaturated, branched and/or unbranched alcohols having a chain length of from 3 to 30 carbon atoms. Such ester oils can then advantageously be selected from the group consisting of isopropyl myristate, isopropyl palmitate, isopropyl stearate, isopropyl oleate, n-butyl stearate, n-hexyl laurate, n-decyl oleate, isooctyl stearate, isononyl stearate, isononyl isononanoate, 2-ethylhexyl palmitate, 2-ethylhexyl laurate, 2-hexyldecyl stearate, 2-octyldodecyl palmitate, oleyl oleate, oleyl erucate, erucyl oleate, erucyl erucate and synthetic, semi-synthetic and natural mixtures of

such esters, e.g. jojoba oil.

DETD **Hydrodispersion** Gel
DETD **Hydrogel**
PI US 6153204 20001128
WO 9744009 19971127

application.

ACCESSION NUMBER:	2002:99473 USPATFULL
TITLE:	Pharmaceutical preparation containing at least folic acid or a folate and tetrahydrobiopterin (bh4) or derivatives thereof used for treating or preventing cardiovascular or neurological disorders by modulating of the activity of nitric oxide synthase (nos)
INVENTOR(S):	Rabelink, Ton J., Utrecht, NETHERLANDS Moser, Rudolf, Schaffhausen, SWITZERLAND

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002052374	A1	20020502	
	US 6544994	B2	20030408	
APPLICATION INFO.:	US 2000-588301	A1	20000607	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 140

L173 ANSWER 3 OF 3 USPATFULL

AB The present invention relates to the compound 5,10-methylene-**tetrahydrofolate** (CH.sub.2 FH.sub.4), and its solution product isomer FH.sub.4, therapeutic uses of these compounds, and compositions thereof. CH.sub.2 FH.sub.4 and FH.sub.4 strongly modulate the in vivo antitumor effects of 5-Fluorouracil.

DETD The applications for CH.sub.2 FH.sub.4 or FH.sub.4 are quite significant and far-reaching. For example, antitumor uses of CH.sub.2 FH.sub.4 or FH.sub.4, combined with TS-inhibitory fluoropyrimidines include: 1) addition to Platinol/5-FU infusion therapy in head and neck cancer and other epidermoid cancers, 2) addition to combination cyclophosphamide/doxorubicin/5-FU in breast cancer 3) addition to **topical** Efudex.RTM. (5-FU) cream under an air-free occlusive dressing for skin conditions (for example benign keratoses, keratoacanthomas, verrucae, premalignant keratoses, in situ cancer and invasive superficial malignancies amenable to **topical** therapy). Furthermore, CH.sub.2 FH.sub.4 or FH.sub.4 can also be applied to those cancer types in which 5-FU and floxuridine are typically combined with LV, such as in colon, rectal and pancreatic carcinomas.

CLM What is claimed is:

6. In a method of inhibiting the growth of a tumor in a patient by administering 5-FU to said patient, the improvement comprising administering (6R,S)-**tetrahydrofolate** (FH.sub.4) in an amount sufficient in combination with the 5-FU as active agents to achieve substantially complete inhibition of thymidylate synthase (TS) in a patient with a tumor sensitive to said combination of active agents.

ACCESSION NUMBER:	94:113021 USPATFULL
TITLE:	5,10-methylene-tetrahydrofolate as a modulator of a chemotherapeutic agent
INVENTOR(S):	Spears, Colin P., Glendale, CA, United States Gustavsson, Bengt G., Gothenburg, Sweden
PATENT ASSIGNEE(S):	University of Southern California, Los Angeles, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5376658		19941227
APPLICATION INFO.:	US 1993-174571		19931223 (8)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1991-789729, filed on 12 Nov 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-521712, filed on 11 May 1990, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Cintins, Marianne M.
ASSISTANT EXAMINER:	Criares, T. J.
LEGAL REPRESENTATIVE:	Robbins, Berliner & Carson
NUMBER OF CLAIMS:	26
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT:	1614

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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CLM What is claimed is:

1. A method of decreasing homocysteine levels in the human body comprising administering at least one **tetrahydrofolate** in natural stereoisomeric form to a human subject.

2. A method of preventing or treating disease associated with increased levels of homocyteine levels in the human body comprising administering at least one **tetrahydrofolate** in natural stereoisomeric form to a human subject.

4. A method of preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels comprising administering at least one **tetrahydrofolate** in natural stereoisomeric form to a female human subject.

5. A method according to claim 2, wherein the **tetrahydrofolate** is 5-formyl-(6S)-**tetrahydrofolic acid**, 5-methyl-(6S)-**tetrahydrofolic acid**, 5,10-methylene-(6R)-**tetrahydrofolic acid**, 5,10-methenyl-(6R)-**tetrahydrofolic acid**, 10-formyl-(6R)-**tetrahydrofolic acid**, 5-formimino-(6S)-**tetrahydrofolic acid** or (6S)-**tetrahydrofolic acid**, or salts thereof.

6. A method according to claim 3, wherein the **tetrahydrofolate** is 5-formyl-(6S)- **tetrahydrofolic acid**, 5-methyl-(6S)-**tetrahydrofolic acid**, 5,10-methylene-(6R)-**tetrahydrofolic acid**, 5,10-methenyl-(6R)-**tetrahydrofolic acid**, 10-formyl-(6R)-**tetrahydrofolic acid**, 5-formimino-(6S)-**tetrahydrofolic acid** or (6S)-**tetrahydrofolic acid**, or salts thereof.

7. A method according to claim 4, wherein the **tetrahydrofolate** is 5-formyl-(6S)-**tetrahydrofolic acid**, 5-methyl-(6S)-**tetrahydrofolic acid**, 5,10-methylene-(6R)-**tetrahydrofolic acid**, 5,10-methenyl-(6R)-**tetrahydrofolic acid**, 10-formyl-(6R)-**tetrahydrofolic acid**, 5-formimino-(6S)-**tetrahydrofolic acid** or (6S)-**tetrahydrofolic acid**, or salts thereof.

8. A method according to claim 2, wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

9. A method according to claim 3, wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

10. A method according to claim 4, wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

11. A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

12. A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with methylene **tetrahydrofolate** reductase deficiency and wherein the

tetrahydrofolate is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

13. A method according to claim 4, wherein increased levels of homocysteine in the human body are associated with methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

14. A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

15. A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

16. A method according to claim 4, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

17. A method according to claim 4, wherein the **tetrahydrofolate** is administered prior to conception.

18. A method according to claim 4, wherein the **tetrahydrofolate** is administered after conception.

19. A method according to claim 5, wherein the **tetrahydrofolate** is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.

21. A method according to claim 11, wherein the **tetrahydrofolate** is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.

ACCESSION NUMBER: 2000:1883 USPATFULL

TITLE: Use of tetrahydrofolates in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine

INVENTOR(S): Muller, Hans Rudolf, Schaffhausen, Switzerland
Ulmann, Martin, Dachsen, Switzerland
Moser, Rudolf, Schaffhausen, Switzerland

PATENT ASSIGNEE(S): Eprova AG, Schaffhausen, Switzerland (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6011040		20000104	
APPLICATION INFO.:	US 1998-95572		19980611	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	CH 1997-1456	19970613

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Henley, III, Raymond
LEGAL REPRESENTATIVE:	Millen, White, Zelano, & Branigan, P.C.
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
LINE COUNT:	360

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the use of **tetrahydrofolates** in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine. Clinical areas of application include all anomalies of the homocysteine level, particularly the prevention and treatment of cardiovascular diseases and the prevention of neural tube deficiencies. The present invention also relates to pharmaceutical preparations comprising at least one compound selected from the group consisting of 5-formyl-(6S)-**tetrahydrofolic acid**, 5-methyl-(6S)-**tetrahydrofolic acid**, 5,10-methylene-(6R)-**tetrahydrofolic acid**, 5,10-methenyl-(6R)-**tetrahydrofolic acid**, 10-formyl-(6R)-**tetrahydrofolic acid**, 5-formimino-(6S)-tetrahydrofolic acid or (6S)-**tetrahydrofolic acid** or pharmaceutically compatible salts thereof, together with pharmaceutically compatible active and adjuvant substances, for influencing the homocysteine level, particularly when a methylene **tetrahydrofolate** reductase deficiency exists, such as when thermolabile methylene **tetrahydrofolate** reductase exists for example.

SUMM The expression "pharmaceutical preparations" refers to enteral (e.g. oral, sublingual or rectal), parenteral or **topical** (e.g. transdermal) forms. Organic or inorganic substances which do not react with the active ingredient can be used as supports, e.g. water, oil, benzyl alcohol, polyethylene glycol, glycerol triacetate or other fatty acid glycerides, gelatine, lecithin, cyclodextrin, carbohydrates such as lactobiose or starch, magnesium stearate, talc or cellulose. Tablets, dragees, capsules powders, syrup concentrates or drops are preferred for oral application, suppositories are preferred for rectal application, and water- or oil-based solutions or lyophilisates are preferably used for parenteral application.

SUMM Suspensions, emulsions or implants can also be used, and patches or creams can be used for **topical** application.

CLM What is claimed is:

1. A method of decreasing homocysteine levels in the human body comprising administering at least one **tetrahydrofolate** in natural stereoisomeric form to a human subject.

2. A method of preventing or treating disease associated with increased levels of homocyteine levels in the human body comprising administering at least one **tetrahydrofolate** in natural stereoisomeric form to a human subject.

4. A method of preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels comprising administering at least one **tetrahydrofolate** in natural stereoisomeric form to a female human subject.

5. A method according to claim 2, wherein the **tetrahydrofolate** is 5-formyl-(6S)-**tetrahydrofolic acid**, 5-methyl-(6S)-**tetrahydrofolic acid**, 5,10-methylene-(6R)-**tetrahydrofolic acid**, 5,10-methenyl-(6R)-**tetrahydrofolic acid**, 10-formyl-(6R)-**tetrahydrofolic acid**, 5-formimino-(6S)-**tetrahydrofolic acid** or (6S)-**tetrahydrofolic acid**, or salts thereof.

6. A method according to claim 3, wherein the **tetrahydrofolate** is 5-formyl-(6S)- **tetrahydrofolic acid**, 5-methyl-(6S)-**tetrahydrofolic acid**,

5,10-methylene-(6R)-**tetrahydrofolic acid**,
5,10-methenyl-(6R)-**tetrahydrofolic acid**,
10-formyl-(6R)-**tetrahydrofolic acid**,
5-formimino-(6S)-**tetrahydrofolic acid** or (6S)-**tetrahydrofolic acid**, or salts thereof.

7. A method according to claim 4, wherein the **tetrahydrofolate** is 5-formyl-(6S)-**tetrahydrofolic acid**,
5-methyl-(6S)-**tetrahydrofolic acid**,
5,10-methylene-(6R)-**tetrahydrofolic acid**,
5,10-methenyl-(6R)-**tetrahydrofolic acid**,
10-formyl-(6R)-**tetrahydrofolic acid**,
5-formimino-(6S)-**tetrahydrofolic acid** or (6S)-**tetrahydrofolic acid**, or salts thereof.

8. A method according to claim 2, wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

9. A method according to claim 3, wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

10. A method according to claim 4, wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

11. A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

12. A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

13. A method according to claim 4, wherein increased levels of homocysteine in the human body are associated with methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

14. A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

15. A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

16. A method according to claim 4, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene **tetrahydrofolate** reductase deficiency and wherein the **tetrahydrofolate** is 5-methyl-(6S)-**tetrahydrofolic acid**, or a salt thereof.

17. A method according to claim 4, wherein the **tetrahydrofolate**

is administered prior to conception.

18. A method according to claim 4, wherein the **tetrahydrofolate** is administered after conception.

19. A method according to claim 5, wherein the **tetrahydrofolate** is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.

21. A method according to claim 11, wherein the **tetrahydrofolate** is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.

ACCESSION NUMBER:	2000:1883 USPATFULL
TITLE:	Use of tetrahydrofolates in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine
INVENTOR(S):	Muller, Hans Rudolf, Schaffhausen, Switzerland Ulmann, Martin, Dachsen, Switzerland Moser, Rudolf, Schaffhausen, Switzerland
PATENT ASSIGNEE(S):	Eprova AG, Schaffhausen, Switzerland (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6011040		20000104
APPLICATION INFO.:	US 1998-95572		19980611 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	CH 1997-1456	19970613

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PRIMARY EXAMINER:	Henley, III, Raymond
LEGAL REPRESENTATIVE:	Millen, White, Zelano, & Branigan, P.C.
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
LINE COUNT:	360

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L181 ANSWER 1 OF 23 USPATFULL

AB Methods for identifying compounds that are inhibitors of bacterial **tetrahydrofolate** biosynthesis are disclosed. Such compounds can be used as lead compounds in methods for preparing antibacterial agents for treating bacterial infections (e.g., in humans, animals, and plants). The disclosed methods allow for high throughput screening of libraries of test compounds.

DETD [0046] A **topical** semi-solid ointment formulation typically contains a concentration of the active ingredient from about 0.1 to 20% wt/vol (e.g., 0.1 to 2% wt/vol of essentially pure material) in a carrier such as a pharmaceutical cream base. Various formulations for **topical** use include drops, tinctures, lotions, creams, solutions, and ointments containing the active ingredient and various supports and vehicles.

ACCESSION NUMBER: 2002:294559 USPATFULL
TITLE: High throughput screen for inhibitors of the folate biosynthetic pathway in bacteria
INVENTOR(S): Murphy, Christopher K., Upton, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164602	A1	20021107
APPLICATION INFO.:	US 2001-925824	A1	20010809 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-224925P	20000811 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: J. PETER FASSE, Fish & Richardson P.C., 225 Franklin Street, Boston, MA, 02110-2804
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1000
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L181 ANSWER 2 OF 23 USPATFULL

AB The present invention relates to the compound 5,10-methylene-**tetrahydrofolate** (CH.sub.2 FH.sub.4), and its solution product isomer FH.sub.4, therapeutic uses of these compounds, and compositions thereof. CH.sub.2 FH.sub.4 and FH.sub.4 strongly modulate the in vivo antitumor effects of 5-Fluorouracil.

DETD The applications for CH.sub.2 FH.sub.4 or FH.sub.4 are quite significant and far-reaching. For example, antitumor uses of CH.sub.2 FH.sub.4 or FH.sub.4, combined with TS-inhibitory fluoropyrimidines include: 1) addition to Platinol/5-FU infusion therapy in head and neck cancer and other epidermoid cancers, 2) addition to combination cyclophosphamide/doxorubicin/5-FU in breast cancer 3) addition to **topical** Efudex.RTM. (5-FU) cream under an air-free occlusive dressing for skin conditions (for example benign keratoses, keratoacanthomas, verrucae, premalignant keratoses, in situ cancer and invasive superficial malignancies amenable to **topical** therapy). Furthermore, CH.sub.2 FH.sub.4 or FH.sub.4 can also be applied to those cancer types in which 5-FU and floxuridine are typically combined with LV, such as in colon, rectal and pancreatic carcinomas.

ACCESSION NUMBER: 96:60704 USPATFULL
TITLE: 5,10,-methylene-tetrahydrofolate as a modulator of a chemotherapeutic agent
INVENTOR(S): Spears, Colin P., Glendale, CA, United States
Gustavsson, Bengt G., Goteborg, Sweden
PATENT ASSIGNEE(S): University of Southern California, Los Angeles, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5534519		19960709
APPLICATION INFO.:	US 1994-326414		19941020 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1993-174571, filed on 23 Dec 1993, now patented, Pat. No. US 5376658 which is a continuation of Ser. No. US 1991-789729, filed on 12 Nov 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-521712, filed on 11 May 1990, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1440
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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000-10062401 20001214

L49 ANSWER 12 OF 17 EUROPATFULL COPYRIGHT 2003 WILA
DETDEN. . . . example vinblastine, vindesine, etoposide and teniposide; antibiotics, for example dactinomycin, doxorubicin, daunorubicin and mitomycin; antimetabolites, for example methotrexate, methotrexate with **leucovorin**, 5-fluorouracil, 6-mecaptopurine, 6-thioguanine, cytarabine, 5-azacytidine and hydroxyurea; alkylating agents, for example nitrogen mustards, mechlorethamine, cyclophosphamide, melphalan, uracil mustard and chlorambucil;. . .
Bally . . . teaches liposomes which encapsulate a medium having a concentration of one or more charged species. This medium is also the **external** medium of the liposome. The original **external** medium is replaced by a one having a different concentration of the one or more charged species. The transmembrane potential. . . enhancing agent , such as an ionophore, added to the bathing medium. Next the antineoplastic agent is added to the **external** medium and the transmembrane potential loads the agent into the liposome. The rate of release of the agent can be. . .
Mayer et al. is directed to a liposome **composition** of an antineoplastic agent and a lipid wherein the liposomes have a transmembrane ion gradient. The liposomes contain a release-inhibition buffer such as citric acid/sodium carbonate. The **compositions** are prepared by first forming the liposomes in an acidic buffer aqueous environment, alkalinizing the **external** medium of the liposomes with a base and adding the resultant liposomes to a antineoplastic agent. After a brief period. . .
Madden et al. discloses **compositions** having a pH gradient which exhibit markedly increased accumulation of pharmaceutical agents above that expected from the Henderson-Hasselbach relationship by formulating the liposomes utilizing a first internal aqueous buffer and a second **external** aqueous buffer wherein the concentration of the pharmaceutical agent exceeds its solubility product in the internal buffer following uptake. The. . .
CLMEN. . . 6-thioguanine, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, semustine, carboplatin, thiotepa, ifosfamide, mesna, amsacrine, mitoxanthrone, or methotrexate with **leucovorin**, preferably wherein the antineoplastic agent is doxorubicin.

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 546951 EUROPATFULL EW 199324 FS OS STA B
TITLE: Combination of liposome encapsulated antineoplastic agents, such as doxorubicin with colony stimulating factors.
Kombination von im Liposomen verkapselten antineoplastischen Mitteln wie Doxorubicin, mit Kolonie-stimulierenden Faktoren.
Combinaison d'agents antineoplastiques, tels que la doxorubicine, encapsules dans des liposomes, avec des tacteurs de stimulation de colonies.
INVENTOR(S): Ostro, Marc J., 23 West Shore Drive, Pennington, New Jersey 08534, US
PATENT ASSIGNEE(S): THE LIPOSOME COMPANY, INC., One Research Way Princeton Forrestal Center, Princeton, NJ 08540, US
PATENT ASSIGNEE NO: 536921
AGENT: Warcoin, Jacques et al, Cabinet Regimbeau 26, avenue Kleber, F-75116 Paris, FR
AGENT NUMBER: 19071
OTHER SOURCE: ESP1993042 EP 0546951 A1 930616
SOURCE: Wila-EPZ-1993-H24-T1b
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch

DESIGNATED STATES:	R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PATENT INFO.PUB.TYPE:	EPA1 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:	

PATENT NO	KIND	DATE
EP 546951	A1	19930616

'OFFENLEGUNGS' DATE:		19930616
APPLICATION INFO.:	EP 1992-403374	19921211
PRIORITY APPLN. INFO.:	US 1991-807116	19911213
	US 1992-988164	19921209

L56 ANSWER 11 OF 11 USPATFULL

DETD The pharmaceutical **compositions** of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be **topical** (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

DETD 5-Methyl-**tetrahydrofolic** acid conjugated 5-methyluridine (32)

CLM What is claimed is:

10. The compound of claim 1 wherein E.sub.2 is a linked folic acid or 5-methyl-**tetrahydrofolic** acid moiety.

22. The oligomeric compound of claim 15 wherein E.sub.2 is a linked folic acid or 5-methyl-**tetrahydrofolic** acid moiety.

ACCESSION NUMBER:	2000:153832 USPATFULL
TITLE:	2'-O-acetamido modified monomers and oligomers
INVENTOR(S):	Manoharan, Muthiah, Carlsbad, CA, United States Kawasaki, Andrew M., Carlsbad, CA, United States Cook, Phillip Dan, Fallbrook, CA, United States Fraser, Allister S., Carlsbad, CA, United States Prakash, Thazha P., Carlsbad, CA, United States
PATENT ASSIGNEE(S):	Isis Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6147200		20001114
APPLICATION INFO.:	US 1999-378568		19990819 (9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Geist, Gary
ASSISTANT EXAMINER:	Crane, L. Eric
LEGAL REPRESENTATIVE:	Woodcock Washburn Kurtz Mackieicz & Norris LLP
NUMBER OF CLAIMS:	46
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	2700

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

L56 ANSWER 8 OF 11 USPATFULL

DETD [0079] Also suitable are cytotoxic agents such as epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; **leucovorin**; tegafur; and haematopoietic growth factors.

DETD [0080] Additional anti-proliferative cytotoxic agents include, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, topotecan, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins. Preferred classes of antiproliferative cytotoxic agents are the EGFR inhibitors, Her-2 inhibitors, CDK inhibitors, and Herceptin.RTM. (trastuzumab). Some especially preferred anti-proliferative cytostatic agents are paclitaxel, cis-platin, carboplatin, epothilones, gemcytabine, CPT-11,5-fluorouracil, tegafur, **leucovorin**, and EGFR inhibitors such as Iressa.RTM. (ZD 1839, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-(3-(4-morpholinyl)propoxy)quinazoline and OSI-774 (4-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)quinazoline).

DETD [0137] The present invention also encompasses a pharmaceutical **composition** useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the combinations of this invention, with or without pharmaceutically acceptable carriers or diluents. The synergistic pharmaceutical **compositions** of this invention comprise an optional anti-proliferative cytotoxic agent or agents, an optional quiescence agent, a formula I compound, and a pharmaceutically acceptable carrier. The methods entail the use of a cytotoxic and/or a cytostatic agent in combination with a formula I compound. The **compositions** of the present invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like. The antineoplastic agents, optional cytostatic agents (if chemical), formula I compounds and **compositions** of the present invention may be administered orally or parenterally including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and **topical** routes of administration.

DETD [0145] Table I sets forth preferred chemotherapeutic combinations and exemplary dosages for use in the methods of the present invention. Where "Compound of Formula I" appears, any of the variations of Formula I set forth herein are contemplated for use in the chemotherapeutic combinations. Preferably, Compound 2 is employed.

CHEMOTHERAPEUTIC COMBINATION	DOSAGE mg/m.sup.2 (per dose)
Compound of Formula I	2.5-750 mg/m2
+ Cisplatin	5-150 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Carboplatin	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Radiation	200-8000 cGy
Compound of Formula I	2.5-750 mg/m2
+ CPT-11	5-400 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Paclitaxel	40-250 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Paclitaxel	40-250 mg/m2
+ Carboplatin	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ 5FU and optionally	5-5000 mg/m2

+ **Leucovorin**	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Epothilone	1-500 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Gemcitabine	100-3000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ UFT and optionally	50-800 mg/m2
+ **leucovorin**	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Gemoitabine	100-3000 mg/m2
+ Cisplatin	5-150 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ UFT	50-800 mg/m2
+ **Leucovorin**	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Cisplatin	5-150 mg/m2
+ paclitaxel	40-250 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Cisplatin	5-150 mg/m2
+ 5FU	5-5000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Oxaliplatin	5-200 mg/m2
+ CPT-11	4-400 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ 5FU	5-5000 mg/m2
+ CPT-11 and optionally	4-400 mg/m2
+ **leucovorin**	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ 5FU	5-5000 mg/m2
+ radiation	200-8000 cGy
Compound of Formula I	2.5-750 mg/m2
+ radiation	200-8000 cGy
+ 5FU	5-5000 mg/m2
+ Cisplatin	5-150 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ Oxaliplatin	5-200 mg/m2
+ 5FU and optionally	5-5000 mg/m2
+ **Leucovorin**	5-1000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ paclitaxel	40-250 mg/m2
+ CPT-11	4-400 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ paclitaxel	40-250 mg/m2
+ 5-FU	5-5000 mg/m2
Compound of Formula I	2.5-750 mg/m2
+ UFT	50-800 mg/m2
+ CPT-11 and optionally	4-400 mg/m2
+ **leucovorin**	5-1000 mg/m2

DETD [0146] In the above Table I, "5FU" denotes 5-fluorouracil, "**Leucovorin**" can be employed as **leucovorin** calcium, "UFT" is a 1:4 molar ratio of tegafur:uracil, and "Epothilone" is preferably a compound described in WO 99/02514 or WO 00/50423, both incorporated by reference herein in their entirety.

DETD [0147] While Table I provides exemplary dosage ranges of the Formula I compounds and certain anticancer agents of the invention, when formulating the pharmaceutical compositions of the invention the clinician may utilize preferred dosages as warranted by the condition of the patient being treated. For example, Compound 2, a compound of Formula I, may preferably be administered at a dosage ranging from about 25-500 mg/m2 every three weeks for as long as treatment is required. Preferred dosages for cisplatin are about 75-120 mg/m2 administered every three weeks. Preferred dosages for carboplatin are within the range of about 200-600 mg/m2 or an AUC of about 0.5-8 mg/ml.times.min; most preferred is an AUC of about 4-6 mg/ml.times.min. When the method

employed utilizes radiation, preferred dosages are within the range of about 200-6000 cGY. Preferred dosages for CPT-11 are within about 100-125 mg/m2, once a week. Preferred dosages for paclitaxel are about 130-225 mg/m2 every 21 days. Preferred dosages for gemcitabine are within the range of about 80-1500 mg/m2 administered weekly. Preferably UFT is used within a range of about 300-400 mg/m2 per day when combined with **leucovorin** administration. Preferred dosages for **leucovorin** are about 10-600 mg/m2 administered weekly.

CLM What is claimed is:

40. The composition according to claim 22 wherein the cytotoxic agent is one or more cytotoxic agents chosen from the group consisting of paclitaxel, cis-platin, carboplatin, gemcytabine, CPT-11, **leucovorin**, tegafur, uracil, 5-fluorouracil, 4-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)quinazoline, and 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-(3-(4-morpholinyl)propoxy)quinazoline).

ACCESSION NUMBER:	2002:4183 USPATFULL		
TITLE:	Synergistic methods and compositions for treating cancer		
INVENTOR(S):	Lee, Francis Y., Yardley, PA, UNITED STATES		

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002002162	A1	20020103
	US 6537988	B2	20030325
APPLICATION INFO.:	US 2001-817456	A1	20010326 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-192278P	20000327 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION

L56 ANSWER 3 OF 11 USPATFULL

SUMM [0010] A less common use of polyvinylpyrrolidone involves suspending, stabilizing or increasing the viscosity of a **topical** or orally-administered suspension or solution, including emulsions. Examples of such use are described in European Patent Publication No. 214501 A2, published Mar. 18, 1987. When used as a suspending or stabilizing agent, the polyvinylpyrrolidone in the **composition** is present in small amounts, as determined by weight of the **composition**. Typically, the amount of polyvinylpyrrolidone in suspensions or emulsions ranges from less than about 1 wt. % to about 5 wt. % of the formulation. See, Handbook of Pharmaceutical Excipients, 2d edition, American Pharmaceutical Association, 1994, 392-399.

SUMM [0066] When the formulation incorporates an anticancer active agent, the formulation can be used in a method of treating and/or preventing cancer in a patient. The preferred anticancer agent for use in the formulation and method of treating and preventing cancer is an indolinone compound, preferably 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone or 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1H-pyrrol-3-yl]propionic acid. The active agent can be used either alone or co-administered with additional active agents. Examples of active agents suitable for co-administration with a formulation of the present invention include, but are not limited to, vascular endothelial growth factor (VEGF), 5-fluorouracil (5-FU), **leucovorin**, CAMPTOSAR.TM. (irinotecan HCl), epirubicin, taxotere, taxol, carboplatin, gemcitabine, cisplatin, oxaliplatin, 5-azacitidine, and other signal transduction inhibitors, such as HERCEPTIN.RTM. (trastazumab) and IRESSA.RTM. (inhibitor of epidermal growth factor receptor tyrosine kinase (EGFR-TK)), as well as other cytostatics, for example matrix metalloproteinase inhibitors (MMPIs), avB3 inhibitors, FITs, and the like. Moreover, it is possible that additional active agents, particularly anticancer active agents, having suitable properties, for example having similar solubility, can be incorporated into the vehicle of the invention.

CLM What is claimed is:
33. The method of claim 32, wherein the formulation is administered in combination with an active agent selected from the group consisting of vascular endothelial growth factor, 5-fluorouracil, **leucovorin**, irinotecan HCl, epirubicin, taxotere, taxol, carboplatin, gemcitabine, cisplatin, oxaliplatin, 5-azacitidine, a signal transduction inhibitors, a cytostatic compound, and mixtures thereof.

ACCESSION NUMBER:	2002:221063 USPATFULL
TITLE:	Self-emulsifying drug delivery systems for extremely water-insoluble, lipophilic drugs
INVENTOR(S):	Gao, Ping, Portage, MI, UNITED STATES Morozowich, Walter, Kalamazoo, MI, UNITED STATES Shenoy, Narmada, Sunnyvale, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002119198	A1	20020829
APPLICATION INFO.:	US 2001-909691	A1	20010720 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-220376P	20000724 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MARSHALL, GERSTEIN & BORUN, 6300 SEARS

103. An antitumor **composition** comprising a solution of 0.1 mg to about 15.0 mg of 11 hydroxy 7 ethyl camptothecin dissolved in 1 10 parts of dimethylisosorbide or dimethylacetamide, wherein said solution further comprises about 1 10 parts polyoxyethylated castor oil, about 0.1 2parts by weight dehydrated ethyl alcohol USPI and about 0.1 0.9 parts citric acid.
104. An antitumor **composition** comprising a solution of, 0.1 mg to about 15.0 mg of 11 hydroxy 7 methoxy camptothecin dissolved in 1 10 parts of dimethylisosorbide or dimethylacetamide, wherein said solution further comprises about 1 10 parts polyoxyethylated castor oil, about 0.1 2 parts by weight dehydrated ethyl alcohol USP, and about 0.1 0.9 parts citric acid.
105. An 11 hydroxy 7 methoxy camptothecin solution comprising 11 hydroxy 7 methoxy camptothecin dissolved in dimethylisosorbide in the presence of a pharmaceutically acceptable acid.
106. The solution of claim 105 wherein said solution is sterilized and prepared for oral, intrapleural, intrathecal, intracisternal, intravesicular, intraperitoneal, subcutaneous, **topical** or parenteral administration to a patient with cancer.
107. An 11 hydroxy 7 methoxy camptothecin solution comprising 11 hydroxy 7 methoxy camptothecin dissolved in dimethylacetamide in the presence of a pharmaceutically acceptable acid.
108. The solution of claim 107 wherein said solution is sterilized and prepared for oral, intrapleural, intrathecal, intracisternal, intravesicular, intraperitoneal, subcutaneous, **topical** or parenteral administration to a patient with cancer.
109. The solution of claim 60 wherein said solution is sterilized and prepared for oral, intrapleural, intrathecal, intracisternal, intravesicular, intraperitoneal, subcutaneous, **topical** or parenteral administration to a patient with cancer.
110. The solution of claim 61 wherein said solution is sterilized and prepared for oral, intrapleural, intrathecal, intracisternal, intravesicular, intraperitoneal, subcutaneous, **topical** or parenteral administration to a patient with cancer.
111. The solution of claims 65, 67, 70, 77f 84, 86f 92f 94F 9,51 97f 99f 101, 103, 104, 105, and 107 wherein said solution is encapsulated within a hard gelatin capsule.
112. The solution of claims 65, 67f 70j, 77, 84f 86, 92f

94f 95, 97f 99, 101, 103, 104, 105, and 107 wherein said solution is encapsulated within a soft gelatin capsule.
113. A method of co administration of compound 11 hydroxy 7 ethyl camptothecin with CPT 11, topotecan, camptothecin, or 10,11 methylenedioxy camptothecin, using a pharmaceutically acceptable carrier, and wherein the co administration is based on an optimal dosage and schedule.
114. A method of co administration of compound 11 hydroxy 7 methoxy camptothecin with CPT 11, topotecan, camptothecin, or 10,11 methylenedioxy camptothecin, using a pharmaceutically acceptable carrier, and wherein the co administration is based on an optimal dosage and schedule.
115. A method of co administration.of compound 11 hydroxy 7 ethyl camptothecin with a combination of CPT 11

topotecan, camptothecin, and 10,11 methylenedioxy camptothecin, using a pharmaceutically acceptable carrier, and wherein the co administration is based on an optimal dosage and schedule.
116. A method of co administration of compound 11 hydroxy 7 methoxy camptothecin with a combination of CPT lle topotecan, camptothecin, and 10,11 methylenedioxy camptothecin, using a pharmaceutically acceptable carrier, and wherein the co administration is based on an optimal dosage and schedule.
117. A method of treatment of cancer in humans wherein compound 11 hydroxy 7 ethyl camptothecin is dissolved in dimethylisosorbide or dimethylacetamide in the presence. of a pharmaceutically acceptable acid and co administered with additional drugs selected from the group consisting of carmustine, azathioprine, cisplatinum, carboplatin, iproplatin, cyclophosphamide, ifosfamide, etoposide, ara C,,doxorubicin, daunorubicin, nitrogen mustard, 5 fluorouracil, bleomycin, mitomycin C, fluoxy-

mesterone, mechlorethamine, teniposide, hexamethylmelamine, **leucovorin**, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G CSF, GM CSF, erythropoietin, g methylene 10 deazaaminopterin or g methylene 10 ethyl 10 deazaaminopterin, taxol, and 5 azacytidine.
118. A method of treatment of cancer in humans wherein compound 11 hydroxy 7 methoxy camptothecin is dissolved in dimethylisosorbide or dimethylacetamide in the presence of a pharmaceutically acceptable acid and co administered with additional drugs selected from the group consisting of carmustine, azathioprine, cisplatinum, carboplatin, iproplatin, cyclophosphamide, ifosfamide, etoposide, ara C, doxorubicin, daunorubicin, nitrogen mustard, 5 fluorouracil, bleomycin, mitomycin C. fluoxymesterone, mechlorethamine, teniposide, hexamethylmelamine, **leucovorin**, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine,, thioTEPA, amsacrine, G CSF, GM CSF, erythropoietin, g methylene 10 deazaaminopterin or g methylene 10 ethyl 10 deazaaminopterin, taxol, and 5 azacytidine.
119. The antitumor **composition** of claim 71 further comprising polyoxyethylated castor oil wherein the polyoxyethylated castor oil is 1 to 10 parts by weight of polyoxyethylated castor oil.
120. The antitumor **composition** of claim 78 further comprising polyoxyethylated castor oil wherein the polyoxyethylated castor oil is 1 to 10 parts by weight of polyoxyethylated castor oil,
121. The solution of claims 61 or 107 wherein said solution contains from about 0.1 mg to about 10.0 mg activity of said compound per ffil of solution.

ACCESSION NUMBER: 1995028404 PCTFULL ED 20020514
TITLE (ENGLISH): 7,11 DISUBSTITUTED CAMPTOTHECIN DERIVATIVES, FORMULATIONS CONTAINING SUCH DERIVATIVES AND THEIR USE
TITLE (FRENCH): DERIVES DISUBSTITUES DE LA 7,11 CAMPTOTHECINE, FORMULES LES CONTENANT ET LEUR UTILISATION
INVENTOR(S): HAUSHEER, Frederick, Herman;
HARIDAS, Kochat
PATENT ASSIGNEE(S): BIONUMERIK PHARMACEUTICALS, INC.;
LUCAS, Brian, Ronald

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9528404	A1	19951026

DESIGNATED STATES
W: CA JP MX AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1995-EP1220 A 19950331
PRIORITY INFO.: US 1994-8/229,527 19940419

L61 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1996:531717 CAPLUS
DN 125:185856
TI Combination for reducing antimicrobial resistance using a methylation inhibitor in combination with an antibiotic
IN Vermeulen, Nicolaas M. J.; Schwartz, Dennis E.
PA Oridigm Corporation, USA
SO PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06
CC 1-5 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9620010	A1	19960704	WO 1995-US16677	19951215
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5872104	A	19990216	US 1994-364246	19941227
AU 9646045	A1	19960719	AU 1996-46045	19951215
PRAI US 1994-364246		19941227		
WO 1995-US16677		19951215		

AB Methods, combinations of agents, and kits are disclosed for use in killing or inhibiting the growth of microorganisms. Enhanced antimicrobial action is provided by using a methylation inhibitor, as exemplified by using an agent that inhibits methylation or maturation of bacterial RNA in combination with, e.g., a macrolide lincosamide streptogramin B (MLS) antibiotic. The methods and compns. described may be employed to reduce the resistance of susceptible microorganisms to antimicrobial agents and thus to treat animals or patients with infections.
ST antimicrobial resistance antibiotic methylation inhibitor combination
IT Antibiotic resistance
Antibiotics
Bactericides, Disinfectants, and Antiseptics
Biocides
Drug resistance
Pharmaceutical dosage forms
Streptococcus aureus
(antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)
IT Sulfonamides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)
IT Ribonucleic acids
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methylation; antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)
IT Pharmaceutical dosage forms
(liposomes, antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)
IT Antibiotics
(macrolide, antibiotic-methylation inhibitor combination for reducing

antimicrobial resistance)

IT Pharmaceutical dosage forms
(nasal, antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT Pharmaceutical dosage forms
(ophthalmic, antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT Pharmaceutical dosage forms
(oral, antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT Pharmaceutical dosage forms
(parenterals, antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT Amines, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(poly-, synthesis, inhibitors; antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT Pharmaceutical dosage forms
(topical, antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT 52-52-8, Cycloleucine 52-52-8D, Cycloleucine, analogs 54-62-6, Aminopterin 58-61-7, Adenosine, biological studies 58-61-7D, Adenosine, analogs 59-05-2, Methotrexate 63-68-3D, Methionine, analogs 69-33-0, Tubercidin 73-03-0, Cordycepin 73-24-5D, Adenine, derivs. 98-92-0, Nicotinamide 98-92-0D, Nicotinamide, analogs 114-07-8, Erythromycin 154-21-2, Lincomycin 320-67-2, 5-Azacytidine 362-75-4, 2',3'-Isopropylideneadenosine 459-86-9, Methylglyoxal bis(guanyl)hydrazone 524-69-6, Xylosyladenine 547-32-0, Sodium sulfadiazine 606-58-6, Toyocamycin 616-29-5, 1,3-Diaminopropan-2-ol 738-70-5, Trimethoprim 958-09-8, 2'-Deoxyadenosine 979-92-0, S-Adenosylhomocysteine 979-92-0D, S-Adenosylhomocysteine, analogs 1867-73-8, 6-Methylaminopurine riboside 2457-80-9, 5'-Deoxy-5'-(methylthio)adenosine 2520-21-0, Celesticetin 2751-09-9, Troleandomycin 3131-03-1, Streptogramin B 3922-90-5, Oleandomycin **4033-27-6** 4291-63-8, 2-Chlorodeoxyadenosine 5072-26-4, Buthionine sulfoximine 5536-17-4, Ara-A 6027-13-0, Homocysteine 6736-58-9, 3-Deazaadenosine 8025-81-8, Spiramycin 10024-97-2, Nitrous oxide, biological studies 11006-76-1, Pristinamycin 11033-22-0, Coformycin 11033-22-0D, Coformycin, isomers 13073-35-3, Ethionine 13734-58-2 16846-24-5, Josamycin 17039-15-5 18323-44-9, Clindamycin 19186-33-5, Aristeromycin 19186-33-5D, Aristeromycin, analogs 23918-98-1, (D)-Eritadenine 29908-03-0D, S-Adenosylmethionine, analogs and sulfonium derivs. 30918-54-8 35457-80-8, Midecamycin 35834-26-5 35899-54-8 39798-19-1, Adenosine dialdehyde 48047-94-5, .alpha.-Methylornithine 51350-19-7, erythro-9-(2-Hydroxy-3-nonyl)adenine 53228-06-1 54262-83-8 55881-07-7, Miocamycin 57344-98-6, S-Tubercidinylhomocysteine 57344-98-6D, S-Tubercidinylhomocysteine, analogs 57884-84-1, S-Aristeromycinyl-L-homocysteine 57884-84-1D, S-Aristeromycinyl-L-homocysteine, analogs 58316-88-4, 3-Deazaaristeromycin 58944-73-3, Sinefungin 58944-73-3D, Sinefungin, analogs 62013-04-1, Dirithromycin 63813-87-6 66753-47-7, A9145c 69955-43-7 70052-12-9 74014-51-0, Rokitamycin 75880-46-5 80214-83-1, Roxithromycin 80738-43-8, Lincosamide 81103-11-9, Clarithromycin 82664-20-8, Flurithromycin 83905-01-5, Azithromycin 84981-49-7 96684-74-1 102052-95-9, 3-Deazaneplanocin A 109214-84-8 112621-39-3 114635-42-6 117362-81-9, SAPH 3 121548-44-5, Neplanocin 121548-44-5D, Neplanocin, analogs 123642-27-3, MDL 73811 142633-93-0 142697-74-3 143800-82-2 144205-77-6, CGP 39937 144224-28-2 154802-86-5 154802-89-8 169735-91-5 180682-77-3 180682-78-4 180682-79-5 180682-80-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**

(antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT 9002-03-3, Dihydrofolate reductase 9012-40-2, Homocysteine transmethylase 9012-52-6, S-Adenosylmethionine synthetase 9023-62-5, Glutathione synthetase 9024-60-6, Ornithine decarboxylase 9024-77-5, Arginine decarboxylase 9025-54-1, S-Adenosylhomocysteine hydrolase 9026-93-1, Adenosine deaminase 9036-20-8, S-Adenosylmethionine decarboxylase 9055-61-2, Dihydropteroate synthetase 37290-90-7, Methionine synthetase 66676-66-2, RNA methyltransferase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antibiotic-methylation inhibitor combination for reducing antimicrobial resistance)

IT 144205-78-7, CGP 33829
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of)

L61 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 2000:277862 CAPLUS
DN 132:298827
TI Natural composition for the treatment and prevention of depression, containing St. John's wort and folic acid derivatives.
IN Buchholz, Herwig; Dudda, Angela; Meduski, Jerzy
PA Merck Patent G.m.b.H., Germany
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K035-78
ICS A61K035-78; A61K031-505
CC 63-5 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000023089	A1	20000427	WO 1999-EP7556	19991008
	W: CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1121139	A1	20010808	EP 1999-950676	19991008
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002527484	T2	20020827	JP 2000-576863	19991008
PRAI	US 1998-104710P	P	19981019		
	WO 1999-EP7556	W	19991008		

AB A natural compn. comprises St. John's Wort (Hypericum perforatum L.), its exts. of active ingredients and derivs. of dihydro- and tetrahydrofolic acid. This natural formulation is useful for the treatment and prevention of depression with a better effect than the ingredients alone (no clin. data).
ST antidepressant Hypericum folate
IT St.-John's-wort (Hypericum)
(natural compn. for the treatment and prevention of depression, contg. St. John's wort and derivs. of dihydro- and tetrahydrofolic acid)
IT Antidepressants
(natural compn. for the treatment and prevention of depression, contg. St. John's wort and folic acid derivs.)
IT 58-05-9, 5-FormyltetrahydroFolic acid 59-30-3D, Folic acid, derivs. 134-35-0, 5-MethyltetrahydroFolic acid 135-16-0, TetrahydroFolic acid 548-04-9, Hypericin 2800-34-2, 10-FormyltetrahydroFolic acid 3432-99-3, 5,10-MethylenetetrahydroFolic acid **4033-27-6**, DihydroFolic acid 7444-29-3
RL: THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(natural compn. for the treatment and prevention of depression, contg. St. John's wort and folic acid derivs.)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bewicke, C; US 5820867 A 1998
(2) Nutramax Lab Inc; WO 993715

L49 ANSWER 16 OF 17 EUROPATFULL COPYRIGHT 2003 WILA

DETDEN F.sub2.Glu of the formula 3A is a potent, concentration-dependent inhibitor of poly(.gamma.-glutamylation) using [.sup3.H]Glu and either methotrexate (4-NH.sub2.-10-CH.sub3.PteGlu) or **tetrahydrofolate** as substrates. Applicants have determined that F.sub2.Glu acts as an alternate substrate, but in contrast to the previously characterized alternate. . .

F.sub2.Glu of the formula 3A is a potent, concentration-dependent inhibitor of poly(.gamma.-glutamylation) using [.sup3.H]Glu and either methotrexate (4-NH.sub2.-10-CH.sub3.PteGlu) or **tetrahydrofolate** as substrates. Applicants have determined that F.sub2.Glu acts as an alternate substrate, but in contrast to the previously characterized alternate. . .

The . . . those neoplastic diseases which generally are or can be treated with folates and antifolates such as methotrexate, aminopterin, 5,10-dideazafolate and **leucovorin**. Such neoplastic diseases include: leukemias, including but not limited to acute lymphoblastic, chronic lymphocytic, acute myloblastic and chronic mylocytic; carcinomas,. . .

Methotrexate . . . the same as the antipsoriasis dosage, except that when the formula 1 compounds are used in the treatment of psoriasis **topical** application is preferred.

The compounds can be administered alone or in the form of a pharmaceutical **composition** in combination with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and. . .

L49 ANSWER 12 OF 17 EUROPATFULL COPYRIGHT 2003 WILA
DETDEN. . . . example vinblastine, vindesine, etoposide and teniposide; antibiotics, for example dactinomycin, doxorubicin, daunorubicin and mitomycin; antimetabolites, for example methotrexate, methotrexate with **leucovorin**, 5-fluorouracil, 6-mecaptopurine, 6-thioguanine, cytarabine, 5-azacytidine and hydroxyurea; alkylating agents, for example nitrogen mustards, mechlorethamine, cyclophosphamide, melphalan, uracil mustard and chlorambucil;. . .
Bally . . . teaches liposomes which encapsulate a medium having a concentration of one or more charged species. This medium is also the **external** medium of the liposome. The original **external** medium is replaced by a one having a different concentration of the one or more charged species. The transmembrane potential. . . enhancing agent , such as an ionophore, added to the bathing medium. Next the antineoplastic agent is added to the **external** medium and the transmembrane potential loads the agent into the liposome. The rate of release of the agent can be. . .
Mayer et al. is directed to a liposome **composition** of an antineoplastic agent and a lipid wherein the liposomes have a transmembrane ion gradient. The liposomes contain a release-inhibition buffer such as citric acid/sodium carbonate. The **compositions** are prepared by first forming the liposomes in an acidic buffer aqueous environment, alkalinizing the **external** medium of the liposomes with a base and adding the resultant liposomes to a antineoplastic agent. After a brief period. . .
Madden et al. discloses **compositions** having a pH gradient which exhibit markedly increased accumulation of pharmaceutical agents above that expected from the Henderson-Hasselbach relationship by formulating the liposomes utilizing a first internal aqueous buffer and a second **external** aqueous buffer wherein the concentration of the pharmaceutical agent exceeds its solubility product in the internal buffer following uptake. The. . .
CLMEN. . . 6-thioguanine, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, semustine, carboplatin, thiotepa, ifosfamide, mesna, amsacrine, mitoxanthrone, or methotrexate with **leucovorin**, preferably wherein the antineoplastic agent is doxorubicin.

L49 ANSWER 13 OF 17 EUROPATFULL COPYRIGHT 2003 WILA
DETDEN. . . coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a **composition** that they release the active ingredient(s) only, or preferably, in a certain part of the intestinal tract, optionally in a delayed manner. Examples of embedding **compositions** which can be used include polymeric substances and waxes.
Dosage forms for **topical** or transdermal administration of a compound of this invention further include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants. . .
CLMDE 10. Verbindung, die aus der Gruppe gewaehlt ist, die aus folgendem besteht:
[1R,3S]-3-(1'-Adamantyl)-1-aminomethyl-3,4-**dihydro**-5,6-dihydroxy-1H-2-benzopyran;
[1R*,3S*]-3-(1'-Adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1H-2benzopyran;
[1R,3S]-3-(1'-Adamantyl)-3,4-dihydro-5,6-dihydroxy-1-(N-methyl)aminomethyl-1H-2-benzopyran;
[1R,3R]-1-Aminomethyl-3-cyclopentylmethyl-3,4-dihydro-5,6-dihydroxy-1H-2benzopyran;
[1R,3S]1-Aminomethyl-3-cyclooctyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyran;
[1R,3R]-1-Aminomethyl-3-n-butyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyran;
[1R,3R]-3-n-Butyl-3,4-dihydro-5,6-dihydroxy-1(N-methyl)aminomethyl-

1H-2-benzopyran, oder aus einem pharmazeutisch vertraeglichen Salz dieser.
10.. . .

SUMM 4.2. Pharmaceutical **Compositions**

SUMM This invention encompasses pharmaceutically acceptable forms of trimetrexate ascorbate, pharmaceutically acceptable **compositions** comprising trimetrexate ascorbate, and pharmaceutically acceptable **compositions** comprising trimetrexate and ascorbic acid, all of which are collectively referred to as the "pharmaceutical **compositions** of the invention." The pharmaceutical **compositions** of the invention may be solid or liquid, and may be used to prepare solid (e.g., tablet, caplet, capsule, lotion, or creme) and liquid (including aerosol) dosage forms of trimetrexate and/or trimetrexate ascorbate. The pharmaceutical **compositions** and dosage forms may be administered by a variety of routes including, but not limited to, oral, **topical**, transdermal, and mucosal (e.g., nasal, rectal, and vaginal).

SUMM Liquid dosage forms comprising pharmaceutical **compositions** of the invention may be prepared for administration by any route, although the particular route by which a dosage form will be administered can affect its preparation. For example, a liquid dosage form suitable for intravenous administration must be sterile and particulate-free.

SUMM A liquid dosage form of the invention is preferably prepared by dissolving trimetrexate ascorbate, or a pharmaceutically acceptable **composition** comprising trimetrexate ascorbate and/or trimetrexate and ascorbic acid, in a pharmaceutically acceptable diluent. An antioxidant such as monothioglycerol may further be added.

SUMM Sterile and particulate-free dosage forms suitable for parenteral administration (e.g., intravenous) are preferably prepared by sterilizing a liquid **composition** comprising trimetrexate ascorbate and/or trimetrexate and ascorbic acid with a technique such as microfiltration. Microfiltration also helps provide a dosage form that is particulate-free.

SUMM Solid dosage forms comprising pharmaceutical **compositions** of the invention may be prepared for oral, **topical**, transdermal, or mucosal (e.g., nasal, vaginal, or rectal) administration to a patient. Solid dosage forms may also be prepared that can be reconstituted to provide liquid dosage forms suitable for parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), oral, **topical**, transdermal, or mucosal (e.g., nasal, vaginal, or rectal) administration to a patient.

SUMM Whether or not obtained by lyophilization, solid **compositions** of the invention (i.e., trimetrexate ascorbate, **compositions** comprising trimetrexate ascorbate, and **compositions** comprising trimetrexate and ascorbic acid) can be combined as active ingredients in intimate admixtures with pharmaceutically acceptable carriers or excipients according to conventional pharmaceutical compounding techniques. A carrier may take a wide variety of forms depending on the method by which the dosage form will be administered. Typical carriers used for oral formulations include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

SUMM A solid **composition** of the invention may further be administered by controlled release means and/or delivery devices capable of releasing the active ingredient (i.e., trimetrexate) at the rate required to maintain constant pharmacological activity for a desirable period of time. Such dosage forms provide a supply of a drug to the body during a predetermined period of time, and thus maintain drug levels in the therapeutic range for longer periods of time than conventional

non-controlled formulations. Examples of controlled release pharmaceutical **compositions** and delivery devices which can be adapted for the administration of the active ingredients of the present invention are described in U.S. Pat. Nos.: 3,847,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200; 4,008,719; 4,687,610; 4,769,027; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,566; and 5,733,566, the disclosures of which are hereby incorporated by reference.

SUMM Solid pharmaceutical **compositions** may exist as creams or pastes suitable, for example, for **topical**, transdermal, or mucosal administration. These **compositions** may comprise carriers and/or diluents in amounts known to those skilled in the art. Suitable carriers include binders, fillers, disintegrants, and lubricants such those described below.

SUMM Solid pharmaceutical **compositions** of the invention may also be presented as discrete units such as capsules, cachets, or tablets. Such **compositions** may be prepared by any of the methods of pharmacy, but all methods include the step of bringing a trimetrexate **composition** of the invention into association with the carrier. In general, pharmaceutical **compositions** are prepared by uniformly and intimately admixing the active ingredient with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired form if necessary.

SUMM For example, a tablet may be prepared by compression or molding. Compressed tablets may be prepared by compressing in a suitable machine a trimetrexate **composition** of the invention in a free-flowing form such as powder or granules, optionally mixed with a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

SUMM Binders suitable for preparing dosage formulations of the pharmaceutical **compositions** of the invention include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose and mixtures thereof.

SUMM Disintegrants are used to cause the tablet to disintegrate when exposed to an aqueous environment. Too much of a disintegrant will produce tablets which may disintegrate in the bottle due to atmospheric moisture; too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of trimetrexate from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the drug should be used to form solid dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typically, about 0.5 to about 15 weight percent of disintegrant, preferably about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical **composition**.

SUMM Suitable lubricants for use with solid dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame

oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Deaussa Co. of Plano, Tex.), CAB--O--SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Me.), and mixtures thereof. A lubricant may optionally be added, typically in an amount of less than about 1 weight percent of the pharmaceutical **composition**.

SUMM As made clear above, solid dosage forms of the invention can be reconstituted to provide liquid dosage forms suitable for parenteral (e.g., intravenous) administration to a patient. Solid dosage forms suitable for reconstitution preferably contain from about 5 mg to about 3000 mg of trimetrexate and/or trimetrexate ascorbate. A typical dosage form is provided in a container (generally made of Type I glass) capable of maintaining a sterile environment and capable of delivering a vacuum dried product. An example of a suitable container is a vial hermetically sealed by a stopper means such as a sterile rubber closure. The stopper means should provide an appropriate seal and yet allow the introduction of diluent such as sterile Water for Injection, USP, Normal Saline, USP, or 5% Dextrose in Water, USP, for the reconstitution of the desired trimetrexate solution. It is intended that these filled containers allow rapid dissolution of the solid **composition** upon the addition of appropriate sterile diluents to give a sterile solution of desired trimetrexate concentration suitable for intravenous administration to a patient. The size of the container in which a solid dosage form is provided should be large enough to contain the volume of solution to be used for reconstitution. Other characteristics of suitable containers are well known to those skilled in the practice of the pharmaceutical arts.

SUMM The pharmaceutical **compositions** of the invention may be administered by, for example, oral, mucosal, **topical**, or parenteral routes. The route of administration chosen in a particular case will depend on the nature and severity of the condition being treated. For example, oral formulations are most suitable for chronic dosing of trimetrexate, while intravenous formulations are most suitable for acute dosing of trimetrexate.

SUMM The suitable dosage range of a pharmaceutical **composition** of the invention will depend on a variety of factors known to those skilled in the art. These include the nature and severity of the condition or disease being treated, and the species, age and body weight of the patient. The adjunctive administration of other drugs much also be considered. For example, because trimetrexate is metabolized by a P450 enzyme system, drugs that induce or inhibit this drug metabolizing enzyme system may alter trimetrexate plasma concentrations. Examples of such drugs include erythromycin, rifampin, rifabutin, ketoconazole, and fluconazole. Other drugs that may affect trimetrexate metabolism include cimetidine, acetaminophen, and nitrogen-substituted imidazole drugs such as clotrimazole, ketoconazole, and miconazole. Patients taking these drugs in combination with trimetrexate ascorbate should be carefully monitored. Physicians' Desk Reference, 53.sup.rd ed., pp. 3172-3175 (1999).

SUMM This invention is further defined by reference to the following examples, which describe in detail the preparation and stability of **compositions** comprising trimetrexate ascorbate and/or trimetrexate and ascorbic acid. It will be apparent to those skilled in the art that many modifications of the materials and methods described below may bc practiced without departing from the scope of this invention.

DETD High performance liquid chromatography (HPLC) was used to determine the purity and decomposition of trimetrexate in the **compositions** of the invention.

DETD Six different lots of liquid dosage forms comprising pharmaceutical **compositions** of the invention were subjected to stability testing. The lots differed from each other with regard to trimetrexate purity, oxygen content, and monothioglycerol content of the dosage forms they contained. The dosage forms of each lot were tested at 5.degree. C. and 25.degree. C. over time for trimetrexate decomposition according to the method of Example 2.

DETD As evidenced by the data provided above, trimetrexate **compositions** of the invention which contain monothioglycerol degrade more slowly over time than those that do not. It is interesting to note, however, that the measured stability of a dosage form which comprises monothioglycerol does not necessarily increase as the amount of monothioglycerol in it is increased.

DETD Solid dosage forms of pharmaceutical **compositions** of the invention were prepared as follows. These particular solid dosage forms can be reconstituted to provide liquid dosage forms suitable for parenteral administration to patients.

DETD As evidenced by the data provided above, certain trimetrexate **compositions** of the invention degrade more slowly over time that trimetrexate glucuronate formulations.

DETD As evidenced by the data provided above, particular solid trimetrexate **compositions** of the invention degrade more slowly than trimetrexate glucuronate **compositions**.

DETD As evidenced by the data provided above, trimetrexate **compositions** of the invention exhibit superior light stability as compared to trimetrexate glucuronate **compositions**.

CLM What is claimed is:

4. A **composition** comprising trimetrexate ascorbate and a carrier.

5. The **composition** of claim 4 wherein said **composition** is solid.

6. The **composition** of claim 4 wherein said **composition** is liquid.

7. The **composition** of claim 4 which further comprises an antioxidant.

8. The **composition** of claim 7 wherein the antioxidant is selected from group consisting of: acetone sodium bisulfite; bisulfite sodium; butylated hydroxy anisole; butylated hydroxy toluene; cystein; cysteinate HCl; dithionite sodium; gentisic acid; gentisic acid ethanolamine; glutamate monosodium; formaldehyde sulfoxylate sodium; metabisulfite potassium; metabisulfite sodium; monothioglycerol; propyl gallate; sulfite sodium; thioglycolate sodium and ascorbic acid.

9. The **composition** of claim 8 wherein said **composition** is solid and the antioxidant is monothioglycerol.

10. The **composition** of claim 9 wherein said **composition** is solid and the amount of monothioglycerol is from about 5 to about 25 weight percent.

11. The **composition** of claim 10 wherein the amount of monothioglycerol is from about 7.5 to about 20 weight percent.

12. The **composition** of claim 11 wherein the amount of monothioglycerol is from about 10 to about 15 weight percent.

13. The **composition** of claim 8 wherein said

composition is liquid and the antioxidant is monothioglycerol.

14. The **composition** of claim 13 wherein the concentration of monothioglycerol is from about 1 to about 20 mg/ml.

15. The **composition** of claim 14 wherein the concentration of monothioglycerol is from about 2 to about 15 mg/ml.

16. The **composition** of claim 15 wherein the concentration of monothioglycerol is from about 3 to about 10 mg/ml.

17. The **composition** of claim 16 wherein the concentration of monothioglycerol is from about 4 to about 9 mg/ml.

18. The **composition** of claim 17 wherein the concentration of monothioglycerol is about 5 mg/ml.

19. The **composition** of claim 4 wherein said **composition** is a pharmaceutical **composition**.

20. The **composition** of claim 19 wherein said **composition** is sterile.

21. The **composition** of claim 19 which further comprises a pharmaceutically acceptable carrier.

22. The **composition** of claim 21 wherein the pharmaceutically acceptable carrier is an excipient selected from the group consisting of: sodium chloride; citric acid; tartaric acid; gelatin; carbohydrates such as dextrose, sucrose, sorbitol, inositol, dextran, and mannitol; EDTA; DTPA; and mixtures thereof.

23. The **composition** of claim 4 which further comprises a source of reduced folate.

24. The **composition** of claim 23 wherein the source of reduced folate is leucovorin.

25. A **composition** comprising trimetrexate and ascorbic acid.

26. The **composition** of claim 25 wherein said **composition** is thermally stable.

27. The **composition** of claim 25 wherein said **composition** is light stable.

28. The **composition** of claim 25 wherein the molar ratio of trimetrexate to ascorbic acid is from about 1:0.1 to about 1:10.

29. The **composition** of claim 28 wherein the molar ratio of trimetrexate to ascorbic acid is from about 1:1 to about 1:5.

30. The **composition** of claim 29 wherein the molar ratio of trimetrexate to ascorbic acid is from about 1:2 to about 1:4.

31. The **composition** of claim 25 wherein said **composition** is solid.

32. The **composition** of claim 25 wherein said **composition** is liquid.

33. The **composition** of claim 32 which comprises trimetrexate in a concentration of from about 6 to about 18 mg/ml.

34. The **composition** of claim 33 which comprises trimetrexate in a concentration of from about 7 to about 15 mg/ml.

35. The **composition** of claim 34 which comprises trimetrexate in a concentration of from about 8 to about 14 mg/mi.

36. The **composition** of claim 35 which comprises trimetrexate in a concentration of from about 9 to about 13 mg/ml.

37. The **composition** of claim 36 which comprises trimetrexate in a concentration of about 10 mg/ml.

38. The **composition** of claim 32 which comprises ascorbic acid in a concentration of from about 5 to about 50 mg/ml.

39. The **composition** of claim 38 which comprises ascorbic acid in a concentration of from about 10 to about 40 mg/ml.

40. The **composition** of claim 39 which comprises ascorbic acid in a concentration of from about 15 to about 30 mg/ml.

41. The **composition** of claim 40 which comprises ascorbic acid in a concentration of from about 20 to about 25 mg/ml.

42. The **composition** of claim 25 which further comprises an antioxidant.

43. The **composition** of claim 42 wherein the antioxidant is selected from group consisting of: acetone sodium bisulfite; bisulfite sodium; butylated hydroxy anisole butylated hydroxy toluene; cystein; cysteinate HCl; dithionite sodium; gentisic acid; gentisic acid ethanolamine; glutamate monosodium; formaldehyde sulfoxylate sodium; metabisulfite potassium; metabisulfite sodium; monothioglycerol; propyl gallate; sulfite sodium; thioglycolate sodium and ascorbic acid.

44. The **composition** of claim 43 wherein said **composition** is solid and the antioxidant is monothioglycerol.

45. The **composition** of claim 44 wherein the amount of monothioglycerol is from about 5 to about 25 weight percent.

46. The **composition** of claim 45 wherein the amount of monothioglycerol is from about 7.5 to about 20 weight percent.

47. The **composition** of claim 46 wherein the amount of monothioglycerol is from about 10 to about 15 weight percent.

48. The **composition** of claim 43 wherein said **composition** is liquid and the antioxidant is monothioglycerol.

49. The **composition** of claim 48 wherein the concentration of monothioglycerol is from about 1 to about 20 mg/ml.

50. The **composition** of claim 49 wherein the concentration of monothioglycerol is from about 2 to about 15 mg/ml.

51. The **composition** of claim 50 wherein the concentration of monothioglycerol is from about 3 to about 10 mg/ml.

52. The **composition** of claim 51 wherein the concentration of monothioglycerol is from about 4 to about 9 mg/ml.

53. The **composition** of claim 52 wherein the concentration of monothioglycerol is about 5 mg/ml.

54. The **composition** of claim 25 wherein said **composition** is a pharmaceutical **composition**.

55. The **composition** of claim 54 wherein said **composition** is sterile.

56. The **composition** of claim 54 which further comprises a pharmaceutically acceptable carrier.

57. The **composition** of claim 56 wherein the pharmaceutically acceptable carrier is an excipient selected from the group consisting of: sodium chloride; citric acid; tartaric acid; gelatin; carbohydrates such as dextrose, sucrose, sorbitol, inositol, dextran, and mannitol; EDTA; DTPA; and mixtures thereof.

58. The **composition** of claim 25 which further comprises a source of reduced folate.

59. The **composition** of claim 58 wherein the source of reduced folate is leucovorin.

60. A liquid pharmaceutical **composition** comprising trimetrexate wherein said liquid pharmaceutical **composition** forms less than about 5 weight percent of impurities when sealed in a vial and maintained at a temperature of about 40.degree. C. for about one month, said weight percent being based upon the weight of trimetrexate.

61. A liquid pharmaceutical **composition** comprising trimetrexate wherein said liquid pharmaceutical **composition** forms less than about 2 weight percent of impurities when sealed in a vial and maintained at a temperature of about 25.degree. C. for about six months, said weight percent being based upon the weight of trimetrexate.

62. A liquid pharmaceutical **composition** comprising trimetrexate wherein said liquid pharmaceutical **composition** forms less than about 2 weight percent of impurities when sealed in a vial and maintained at a temperature of about 5.degree. C. for about one year, said weight percent being based upon the weight of trimetrexate.

63. The pharmaceutical **composition** of claim 60, 61, or 62 wherein said pharmaceutical **composition** is sterile.

69. A pharmaceutical **composition** which comprises trimetrexate, ascorbic acid, and monothioglycerol.

70. A method of treating a disease or condition associated with **dihydrofolate** reductase activity comprising administering to a subject in need of such treatment a therapeutically effective amount of trimetrexate ascorbate.

71. A method of treating a disease or condition associated with **dihydrofolate** reductase activity comprising administering to a subject in need of such treatment a therapeutically effective amount of a **composition** comprising trimetrexate and ascorbic acid.

72. The method of claim 70 or 71 wherein the disease or condition associated with **dihydrofolate** reductase activity is a viral infection, fungal infection, yeast infection, bacteria infection, protozoa infection, psoriasis, rheumatoid arthritis, abnormal angiogenesis, or cancer.

ACCESSION NUMBER: 2001:107903 USPATFULL

TITLE: **Compositions** comprising trimetrexate and methods of their synthesis and use

INVENTOR(S): Stogniew, Martin, Blue Bell, PA, United States
Zadei, Javad M., West Chester, PA, United States

PATENT ASSIGNEE(S): MedImmune Oncology, Inc., West Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6258821	B1	20010710

L32 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN 2002:462450 CAPLUS
DN 137:37398
TI Use of folic acid and/or its derivatives for the manufacture of **topical compositions**
IN Max, Heiner; Will, Katrin; Schimpf, Ralf; Raschke, Thomas; Hargens, Birgit
PA Beiersdorf A.-G., Germany
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DT Patent
LA German
IC ICM A61K007-00
ICS A61K007-48; A61K007-02; A61K031-505
CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1214927	A1	20020619	EP 2001-129474	20011211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
DE 10062401	A1	20020620	DE 2000-10062401	20001214
JP 2002212077	A2	20020731	JP 2001-378512	20011212
US 2002150601	A1	20021017	US 2001-21627	20011212
PRAI DE 2000-10062401	A	20001214		

AB The use of folic acid and its derivs. for prodn. of cosmetics or dermatol. formulations for prophylaxis or repair of DNA damage in the skin is disclosed. Thus, an oil-in-water cream contains (wt.-%) glyceryl stearate citrate 2.00, stearyl alc. 5.00, caprylic acid/caprinic acid triglyceride 4.00, octyldodecanol 4.00, glycerol 3.00, Carbomer 0.10, folic acid 0.30, EDTA 0.10, sodium hydroxide q.s., preservative q.s., perfume q.s., and demineralized water to 100.00, with pH set to 6.00.
ST folate DNA damage repair skin cosmetic pharmaceutical
IT Cosmetics
(creams; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT DNA
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PYP (Physical process); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(damage to cutaneous; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Cosmetics
Drug delivery systems
(emulsions; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Cosmetics
Drug delivery systems
(lotions; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Cosmetics
(makeups; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Emulsions
(oil-in-water; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Drug delivery systems
(ointments, creams; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Drug delivery systems
(**topical**; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)
IT Cosmetics

DNA repair
Skin
(use of folic acid and/or its derivs. for the manuf. of **topical compns**.)

IT 9003-01-4D, Carbomer, crosslinked
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(carbomer; use of folic acid and/or its derivs. for the manuf. of **topical compns**.)

IT 56-81-5, Glycerol, biological studies 112-92-5, Stearyl alcohol 538-23-8, Glycerol tricaprylate 34513-50-3, Octyldodecanol 100359-41-9, Glycerylstearate citrate
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(use of folic acid and/or its derivs. for the manuf. of **topical compns**.)

IT 59-30-3, Folic acid, biological studies 59-30-3D, Folic acid, derivs. 135-16-0, **Tetrahydrofolic** acid 4033-27-6, **Dihydrofolic** acid
RL: COS (Cosmetic use); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(use of folic acid and/or its derivs. for the manuf. of **topical compns**.)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Barclay, B; WO 0203942 A 2002 CAPLUS
(2) Beiersdorf Ag; DE 4341001 A 1995 CAPLUS
(3) Beiersdorf Ag; DE 19533330 A 1997 CAPLUS
(4) Beiersdorf Ag; EP 1175898 A 2002 CAPLUS
(5) Danielov, M; US 5885974 A 1999 CAPLUS
(6) Jacobson, E; WO 0178660 A 2001 CAPLUS
(7) Revlon Consumer Prod Corp; WO 0064401 A 2000 CAPLUS

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gainst cellular damage caused by UV light)

L63 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 1996:494170 CAPLUS
DN 125:132809
TI Bioactive agent-containing biocomplex for correcting biological information transfer using three biological information blocks
IN Danielov, Michael M.
PA Dns Scientific, Inc., USA
SO PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-21
ICS A61K039-395; A61K031-55; A61K031-44; A61K031-24
CC 1-12 (Pharmacology)
Section cross-reference(s): 2, 62, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9617621	A1	19960613	WO 1995-US15919	19951206
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5885974	A	19990323	US 1994-350234	19941206
	AU 9645108	A1	19960626	AU 1996-45108	19951206
	US 6303588	B1	20011016	US 1999-228384	19990112
PRAI	US 1994-350234	A	19941206		
	WO 1995-US15919	W	19951206		

AB Methods are disclosed for correcting biol. information transfer in a patient in need of such therapy which comprise administration of a compn. comprising a therapeutically effective amt. of a biocomplex comprising .gtoreq.1 bioactive agent from each of the 3 informational blocks of biol. information transfer, each agent present in an amt. sufficient to correct the biol. information transfer of the patient under treatment and resulting in the resumption of normal cell metab., and the amt. being less than the buffering amt. of said agent; together with a carrier therefor.
ST biol information transfer block therapeutic; cell metab information transfer biocomplex therapeutic
IT Acne
Alopecia
Animal cell
Antioxidants
Circulation
Cosmetics
Eczema
Metabolism
Pharmaceutical dosage forms
Pharmaceuticals
Pruritus
Psoriasis
Seborrhea
Signal transduction, biological
Skin, disease
Therapeutics
(bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Albumins, biological studies
Calmodulins
Carbohydrates and Sugars, biological studies

Catecholamines
Cerebrosides
Coenzymes
Collagens, biological studies
Elastins
Gelatins, biological studies
Glycolipids
Lipids, biological studies
Orosomucoids
Peptides, biological studies
Phosphatidic acids
Phosphatidylcholines, biological studies
Phosphatidylethanolamines
Phosphatidylinositols
Phosphatidylserines
Phosphoinositides
Phospholipids, biological studies
Prostaglandins
Protamines
Proteins, biological studies
Sphingolipids
Steroids, biological studies
Sulfatides
Vitamins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Animal growth regulator receptors
Estrogen receptors
Prostaglandin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Brain
(ext.; bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Shock
(post-trauma; bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Cell membrane
(substitute cell membrane delivery system; bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Prostaglandins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Prostaglandins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Prostaglandins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(E, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(animal growth regulator, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Skin
(cellulite, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Glycerides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(di-, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Phosphoinositides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(di-, 4-phosphates, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Skin, disease
(dry, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(estrogen, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Corticosteroid receptors
Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glucocorticosteroid, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Lipoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high-d., bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Phosphatidylcholines, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Elastins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrolyzates, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Lipoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-d., bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Corticosteroid receptors
Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mineralocorticosteroid, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Dermatitis

(neuro-, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Skin, disease
(oily, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Pharmaceutical dosage forms
(ointments, creams, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Pharmaceutical dosage forms
(ophthalmic, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Pharmaceutical dosage forms
(parenterals, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prostaglandin, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Sunburn and Suntan
(suntanning agents, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Pharmaceutical dosage forms
(**topical**, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Injury
(trauma, shock following; bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Phosphoinositides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tri-, 4,5-bis(phosphates), bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Collagens, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type I, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Collagens, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type II, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Collagens, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type III, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Lipoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(very-low-d., bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Skin, disease
(wrinkle, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)
IT Receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.2-adrenergic, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.2-adrenergic, bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT 60-92-4, Cyclic AMP
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(bioactive agent-contg. biocomplex for correcting biol. information transfer and cell metab., and therapeutic use)

IT 50-14-6, Ergocalciferol 50-23-7, Hydrocortisone 50-28-2, .beta.-Estradiol, biological studies 50-81-7, L-Ascorbic acid, biological studies 51-61-6, Dopamine, biological studies 52-39-1, Aldosterone 52-89-1, L-Cysteine hydrochloride 53-59-8, .beta.-NADP 53-84-9, .beta.-NAD 54-47-7, Pyridoxal-5-phosphate 55-31-2, Epinephrine hydrochloride 56-65-5, Adenosine triphosphate, biological studies 56-81-5D, 1,2,3-Propanetriol, 1,2-diacyl derivs. 56-89-3, L-Cystine, biological studies 57-11-4, Octadecanoic acid, biological studies 57-83-0, Progesterone, biological studies 57-87-4, Ergosterol 57-88-5, Cholesterol, biological studies 58-56-0, Pyridoxine hydrochloride 58-85-5, Biotin 58-95-7, .alpha.-Tocopherol acetate 59-30-3, Folic acid, biological studies 60-18-4, L-Tyrosine, biological studies 60-33-3, 9,12-Octadecadienoic acid (Z,Z)-, biological studies 63-91-2, L-Phenylalanine, biological studies 65-71-4, Thymine 66-22-8, Uracil, biological studies 67-03-8, Thiamine hydrochloride 71-30-7, Cytosine 73-22-3, L-Tryptophan, biological studies 73-24-5, Adenine, biological studies 73-40-5, Guanine 79-81-2, Retinol palmitate 85-61-0, Coenzyme A, biological studies 86-01-1, Guanosine triphosphate 96-26-4, Dihydroxyacetone 98-92-0, Nicotinamide 112-85-6, Behenic acid 113-79-1, Arginine vasopressin 117-39-5, Quercetin 122-32-7, Triolein 123-33-1, Maleic hydrazide **135-16-0**, Tetrahydrofolic acid 137-08-6, Pantothenic acid hemicalcium salt 145-42-6, Sodium taurocholate 154-87-0, Cocarboxylase 329-56-6, Arterenol hydrochloride 361-09-1, Sodium cholate 363-24-6, Prostaglandin E2 463-40-1, Linolenic acid 481-39-0, Juglone 506-21-8, Linolelaidic acid 506-30-9, Arachidic acid 537-40-6, Trilinolein 551-11-1, Prostaglandin F2.alpha. 555-43-1, Tristearin 606-68-8 620-64-4, Triarachidin 745-65-3, Prostaglandin E1 863-57-0, Sodium glycocholate 987-65-5, Adenosine triphosphate disodium salt 1105-02-8, Corticosterone-21-sulfate 1184-16-3 1340-08-5, Vitamin P 1407-47-2, Angiotensin 1731-94-8, Nonadecanoic acid methyl ester 2566-90-7 2644-64-6, Dipalmitoylphosphatidylcholine 2752-99-0, Trierucin 3026-45-7, Dipalmitoylphosphatidylethanolamine 4537-76-2, Distearoylphosphatidylethanolamine 4537-77-3, Dipalmitoylphosphatidylglycerol 4537-78-4, Distearoylphosphatidylglycerol 4539-70-2, Distearoylphosphatidylcholine 4999-79-5, Estradiol-3-sulfate sodium salt 6064-90-0, Heneicosanoic acid methyl ester 6610-25-9, Arachidonic acid sodium salt 7235-40-7, .beta.-Carotene 7665-99-8, Cyclic GMP 9001-62-1, Lipase 9002-60-2, Adrenocorticotropic hormone, biological studies 9002-60-2D, Adrenocorticotropic hormone, 1-24 fragment 9002-64-6, Parathyroid hormone 9002-64-6D, Parathyroid hormone, 1-36 fragment 9002-67-9, Luteinizing hormone 9002-68-0, Follicle-stimulating hormone 9002-71-5, Thyrotropic hormone 9002-72-6, Somatotropin 9004-10-8, Insulin, biological studies 9004-61-9, Hyaluronic acid 9005-49-6, Heparin sulfate, biological studies 9007-12-9, Thyrocalcitonin 9007-92-5, Glucagon, biological studies 9015-73-0 9026-43-1, Protein kinase 9041-08-1, Heparin sodium salt 10417-94-4 10529-43-8, Cholecalciferol sulfate 11000-17-2, Vasopressin 11061-68-0, Human insulin

11128-99-7, Angiotensin II 12629-01-5, Human growth hormone 13487-42-8
13699-48-4, Dimyristoylphosphatidylcholine 14465-68-0 15866-84-9,
Adenosine triphosphate calcium salt 18641-57-1, Tribehenin 20255-95-2,
Dimyristoylphosphatidylethanolamine 20290-75-9 22251-85-0, Flavin
mononucleotide sodium salt 24967-93-9, Chondroitin sulfate A
24967-94-0, Dermatan sulfate 25322-46-7, Chondroitin sulfate C
26536-13-0, Trinonadecanoin 27964-99-4, Poly-D-lysine hydrobromide
28845-86-5, 13,16,19-Docosatrienoic acid, (Z,Z,Z)- 28874-58-0
35121-78-9, Prostaglandin I2 37221-79-7, Vasoactive intestinal peptide
37377-93-8, .beta.-Lipotropin 37377-93-8D, .beta.-Lipotropin, fragment
37839-81-9, Cyclic AMP sodium salt 40245-60-1, Cyclic GMP sodium salt
41598-07-6, Prostaglandin D2 52910-82-4, Aldosterone-21-hemisuccinate
55672-92-9, Coenzyme A sodium salt 59392-49-3, Gastric inhibitory
peptide 60617-12-1, .beta.-Endorphin 60617-12-1D, .beta.-Endorphin,
fragment 61361-72-6, Dimyristoylphosphatidylglycerol 61849-14-7,
Prostaglandin I2 sodium salt 78392-27-5, Cholecalciferol sulfate sodium
salt 80380-39-8, Tri-11-eicosenoin 85166-31-0, D-myo-Inositol-1,4,5-
triphosphate 92216-45-0, D-myo-Inositol-2,4,5-triphosphate 96012-99-6,
Guanosine triphosphate lithium salt 99660-95-4 100775-23-3,
Corticosterone-21-sulfate potassium salt 108340-81-4, D-myo-Inositol,
1,4,5-tris(dihydrogen phosphate), hexasodium salt 135271-36-2,
D-myo-Inositol-1,4,5-triphosphate potassium salt
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic
use); BIOL (Biological study); **USES (Uses)**
(bioactive agent-contg. biocomplex for correcting biol. information
transfer and cell metab., and therapeutic use)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(intracellular, mobilization; bioactive agent-contg. biocomplex for
correcting biol. information transfer and cell metab., and therapeutic
use)

=>